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RETICULOENDOTHELIAL GRANULOMATOSIS

Report of Two Cases of Hand-Schüller-Christian Disease

A. J. BLANCHARD, M.D.
AND
F. H. BOONE, M.D.
TORONTO, CANADA

IN MOST of the reviews of the literature on Hand-Schüller-Christian disease, credit is usually given to Hand for the original description of the condition. In 1893, he reported a case which included defects in the skull, exophthalmos and polyuria.[1] Because of the caseous-like quality of the lesions and their granulomatous nature, he considered them to be tuberculous. However, in an earlier report in 1865, Smith of London described a typical example of the condition.[2] He considered the lesions to represent "dried up abscesses." In 1915, Schüller described 3 cases with various symptoms, in each of which were displayed defects in the membranous bones.[3] He presented the cases from the roentgenologic point of view. For 1 case in which there was diabetes insipidus, he suggested a primary pituitary origin. Christian, in 1919, also suggested that the condition was due to a disturbance in pituitary function.[4] After the publication of an article by Rowland in 1928,[5] the view came to be held almost universally that Hand-Schüller-Christian disease is a primary disorder of lipid metabolism, with abnormal storage of cholesterol in the reticuloendothelial system. Accordingly, it was grouped with Neimann-Pick disease and Gaucher's disease as a primary congenital lipodystrophy. In support of this theory, the hypercholesteremia of some of the cases and the xanthomatous nature of the lesions were cited. However, with

From the Pathological Laboratory and Paediatric Service of the Hamilton General Hospital, Hamilton, Ontario, Canada.

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1. Hand, A.: Arch. Pediat. **10**:673, 1893.
2. Smith, T.: Tr. Path. Soc. London **16**:224, 1865.
3. Schüller, A.: Fortschr. a.d. Geb. d. Röntgenstrahlen **23**:12, 1915-1916.
4. Christian, H. A.: Contrib. M. & Biol. Research **1**:390, 1919.
5. Rowland, R. S.: Xanthomatosis and Reticulo-Endothelial System: Correlation of Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), Arch. Int. Med. **42**:611 (Nov.) 1928.

the study of increasing numbers of cases, it was observed that the great majority did not show a significant increase in blood cholesterol and that in the various lesions encountered in a given case foam cells were often a minor feature. Lately, it was suggested[6] that the histologic and biochemical features of the disease best suit the hypothesis that the condition is a primary reticuloendothelial granuloma of unknown origin and that the cholesterol deposition in the granulomas is a secondary occurrence and is not responsible for their formation.

It is the purpose of this communication to present 2 examples of the condition whose features tend to support this newer hypothesis.

REPORT OF CASES

CASE 1.—*Clinical History.*—This 6 month old girl was admitted to the hospital Jan. 4, 1940. The mother stated that the child had been well until five weeks before admission, when a small nonpainful swelling was noticed behind the left ear. The child had seemed listless and irritable, and its skin showed pronounced pallor. Birth and the postnatal period had been uneventful.

Examination revealed an extremely pale, irritable infant with generalized enlargement of the lymph nodes. These nodes were firm, but neither tender nor fixed. The spleen was not palpable. The temperature ranged irregularly from 99.2 to 101.1 F., with increased pulse and respiratory rates.

Laboratory examinations showed severe anemia, with a red blood cell count of 2,080,000 per cubic millimeter, hemoglobin content of 39 per cent and a white blood cell count of 16,800, of which 58 per cent were polymorphonuclear leukocytes, 35 per cent lymphocytes, 3 per cent monocytes and 4 per cent myelocytes. The smear showed many microcytic red blood cells, a few macrocytes and an occasional erythroblast.

No definite diagnosis was made.

A blood transfusion was given; the child was placed on a diet rich in vitamins C and D and discharged from the hospital. On readmission six weeks later, there was no clinical improvement and two lumps were palpable in the skull. Roentgenographic examination revealed numerous areas of rarefaction in the skull, long bones, pelvis, ribs and clavicles. A biopsy specimen was taken from one of the lesions of the skull, and, after considerable study, a diagnosis of Hand-Schüller-Christian disease was made (fig. 1*A*). The sections showed a diffuse granulomatous lesion consisting of proliferating macrophages, many of which exhibited mitotic figures. Some of the macrophages possessed a pale-staining cytoplasm. Multinucleated giant cells, varying numbers of eosinophils, a few polymorphonuclear leukocytes and plasma cells were scattered about. All the tissue was embedded, and none was available for fat stains.

Transfusion was again performed, and the hemoglobin concentration was raised to 50 per cent. The white blood cell count was still elevated to 17,000 per cubic millimeter, with 67 per cent polymorphonuclear leukocytes.

On each of her two subsequent admissions to the hospital, the anemia was progressively more advanced, with hemoglobin values of 42 and 35 per cent. Roent-

6. (*a*) Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of Nonlipoid-Storing Macrophages; Discussion of So-Called Reticulo-Endothelioses, Am. J. Dis. Child. **51**:499 (March) 1936. (*b*) Otani, S., and Ehrlich, J. C.: Am. J. Path. **16**:479, 1940.

genograms revealed an increase in the number and size of the bony lesions. Chemical examination of the blood on one admission revealed a cholesterol value of 110 mg. per hundred cubic centimeters. On an earlier occasion, the serum phosphorus was estimated at 3.66 and the serum calcium at 10.9 mg. per hundred cubic centimeters.

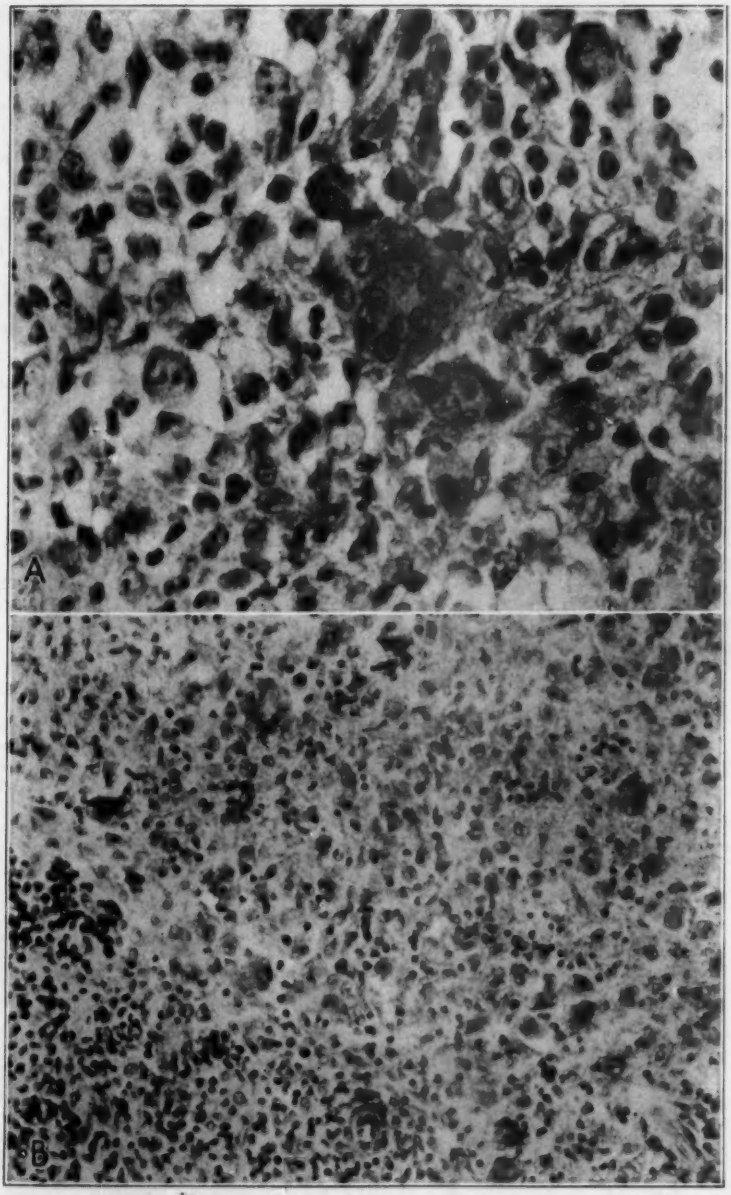

Fig. 1.—Photomicrographs showing changes in Hand-Schüller-Christian disease in a biopsy specimen from a lesion of the skull (*A*, × 500) and in a section of marrow from the femur (*B*, × 220).

Death eventually occurred outside the hospital sixteen and a half months from the onset of symptoms. At no time were there any clinical indications of diabetes insipidus or exophthalmos.

Observations at Autopsy.—The autopsy was restricted to an abdominal examination and the removal of a femur. The body was extremely emaciated, but the cutaneous surface was clear and pale. The liver was of normal size and pale yellow throughout. The spleen was moderately enlarged and showed a mottling of small white areas against a dark purplish red background. The kidneys, pancreas and adrenal glands were grossly normal. The mesenteric lymph nodes were moderately enlarged. The right femur was removed and split longitudinally. The marrow cavity was completely filled with a pale, firm, grayish yellow tissue. In the diaphyses of the bone, there was a considerable loss of the normal bony trabeculae.

Microscopic Examination.—Microscopic examination of the organs showed normal pancreas and adrenal glands, with fatty degeneration of liver and kidneys. Section of the marrow of the femur showed a striking granulomatous infiltration which almost completely replaced the marrow tissue (fig. 1*B*). This infiltration was present in the forms of discrete foci and wide, confluent areas. The granuloma was composed of large reticuloendothelial cells or macrophages, several of which contained two and three nuclei. Some of these macrophages bore a definite resemblance to the Sternberg-Reed cells of Hodgkin's disease. Scattered among the macrophages were small and varying numbers of eosinophils, plasma cells and lymphocytes. In a considerable number of the granulomatous foci the central portions were occupied by areas of necrosis. In none of the sections examined were foam cells distinguishable. Surrounding the granulomatous areas was hyperplastic bone marrow. Here and there throughout the tissue could be seen an occasional trabecula of dead or degenerating bone. Sections of lymph node showed extensive granulomatous areas similar to those seen in the bone marrow, but eosinophils were absent (fig. 2 *A*). Necrosis in the central zones of the foci was pronounced. In many of the foci, multinucleated giant cells of the foreign body type were particularly prominent. Sections of spleen showed small areas similar to those noted in the bone marrow and lymph node. These areas tended to be confined almost entirely to the malpighian bodies and were not present in the pulp (fig. 2 *B*). In frozen sections stained with scarlet red a few fine lipid granules were present within the cytoplasm of the macrophages in some instances. Histologically typical foam cells were not recognized in any of the lesions.

Case 2.—*Clinical History.*—This 2½ year old boy was admitted to the hospital Feb. 22, 1941. For one year prior to admission, the patient had had a generalized, itchy, recurrent cutaneous eruption involving particularly the head, chest and back. The mother was of the opinion that the rash tended to appear with the onset of a running nose. At first, the rash would clear up after a month's time. For the past year, there had been a persistent discharge from both ears. About one week before admission, the rash had suddenly reappeared, and for two days there had been a persistent cough. The birth, family and postnatal history was unremarkable.

Physical examination revealed an irritable child, whose body was covered with a diffuse, reddish, papular rash. The scalp, in addition, was covered with crusting lesions. The cervical and postauricular glands were enlarged but not tender, and the tonsils were hypertrophied. A purulent discharge was coming from the right ear. The breath sounds in the lungs were vesicular, and no rales or rhonchi were heard. The temperature ranged from 99 to 104 F.

Laboratory examination showed the urine to be clear. Examination of the blood revealed a red blood cell count of 5,850,000 per cubic millimeter, hemoglobin content of 36 per cent and a leukocyte count of 17,300, with 63 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes and 1 per cent monocytes.

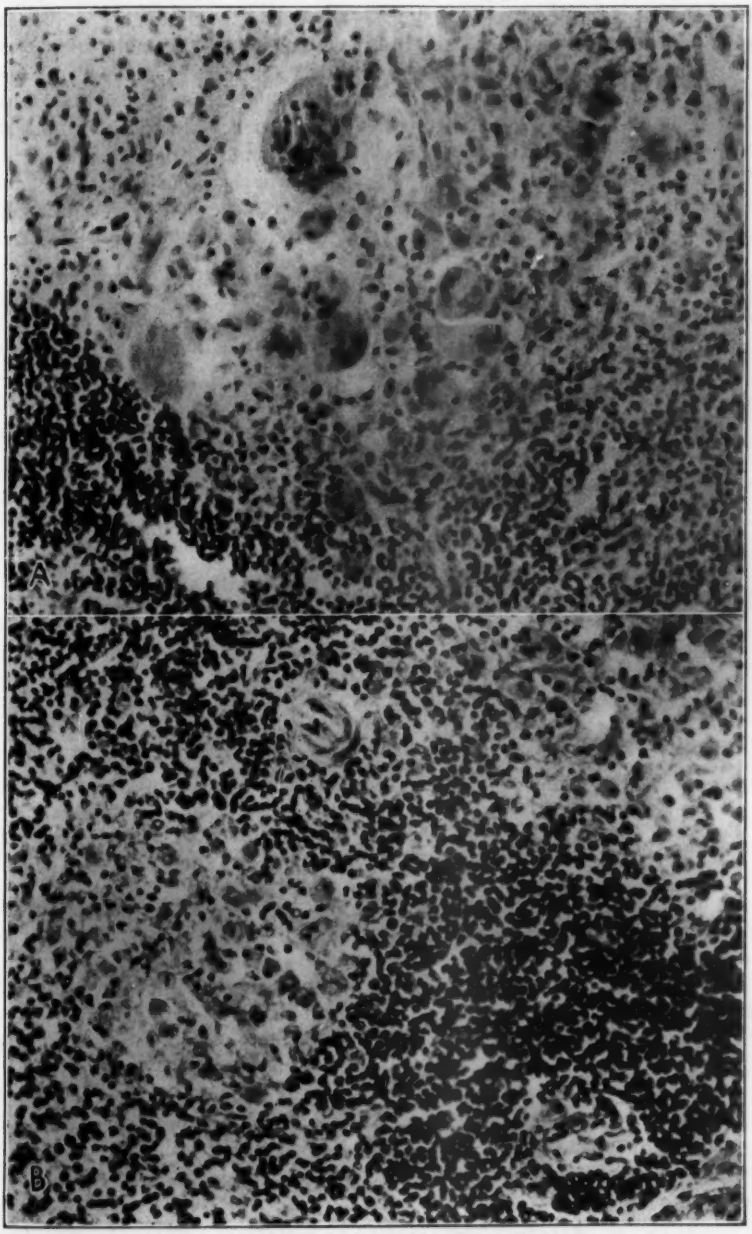

Fig. 2.—Photomicrographs showing extensive granulomatous areas in a section of lymph node (*A* × 220) and in a section of the spleen (*B*, × 220).

After several weeks in the hospital, a mass was noted in the right temporal region of the skull. A biopsy specimen from this area revealed yellowish tissue which microscopically was completely necrotic. At a later date (April 8) roentgenographic examination of the skeleton revealed the presence of numerous destructive lesions of the skull, principally within the parietal and frontal regions and the roofs of the orbital cavities (fig. 3*A*). A mass was palpable in the right axilla, and roentgenogram showed extensive destruction of the midportion of the right fourth rib (fig. 3*B*). A specimen was taken for biopsy (fig. 4*A*), and the destruction was reported as typical of that in Hand-Schüller-Christian disease. The specimen showed a granulomatous lesion with macrophages, multinucleated cells and a few eosinophils, but no foam cells were evident.

Gradually increasing numbers of bony lesions appeared in the right femur, pelvis and mandible. The right eye began to exhibit exophthalmos. Cellulitis developed in the scalp in the region where the biopsy specimen was taken and

Fig. 3.—Roentgenograms (case 2) showing lesions of the skull (*A*) and areas of destruction in the midportion of the right fourth rib and the right femur (*B*).

came to involve the orbit. These areas were opened and continued to drain pus for the remainder of the illness. Staphylococcus aureus later was grown from this exudate.

Chemical examination of the blood on April 24 showed the cholesterol to be raised to 230 mg. per hundred cubic centimeters. A second examination on August 11 showed a normal value of 170 mg. The course of this child's illness went progressively downhill. The cutaneous lesions persisted; the ears and the scalp and orbital lesions continued to drain; coughing became a particularly serious symptom, and during the last weeks of the illness the breathing became increasingly shallow, rapid and labored. At no time during the illness were there clinical indications of diabetes insipidus. Death occurred twenty months after the onset of symptoms.

Observation at Autopsy.—The autopsy revealed an extremely emaciated, dehydrated boy whose cutaneous surface was involved by a red, scaly eruption which showed heavy crusting, particularly of the face and neck. On the hands and feet

were multiple, small red spots resembling petechiae. Two punched-out ulcers were present in the skin of the right temporal region, one measuring 1.5 cm. and the other 0.8 cm. in diameter. These ulcers led down through defects in the bone to the dura mater. The right eyeball was decidedly protuberant, and, at the lateral border of the eye, a fistulous opening communicated with the lesions in the right

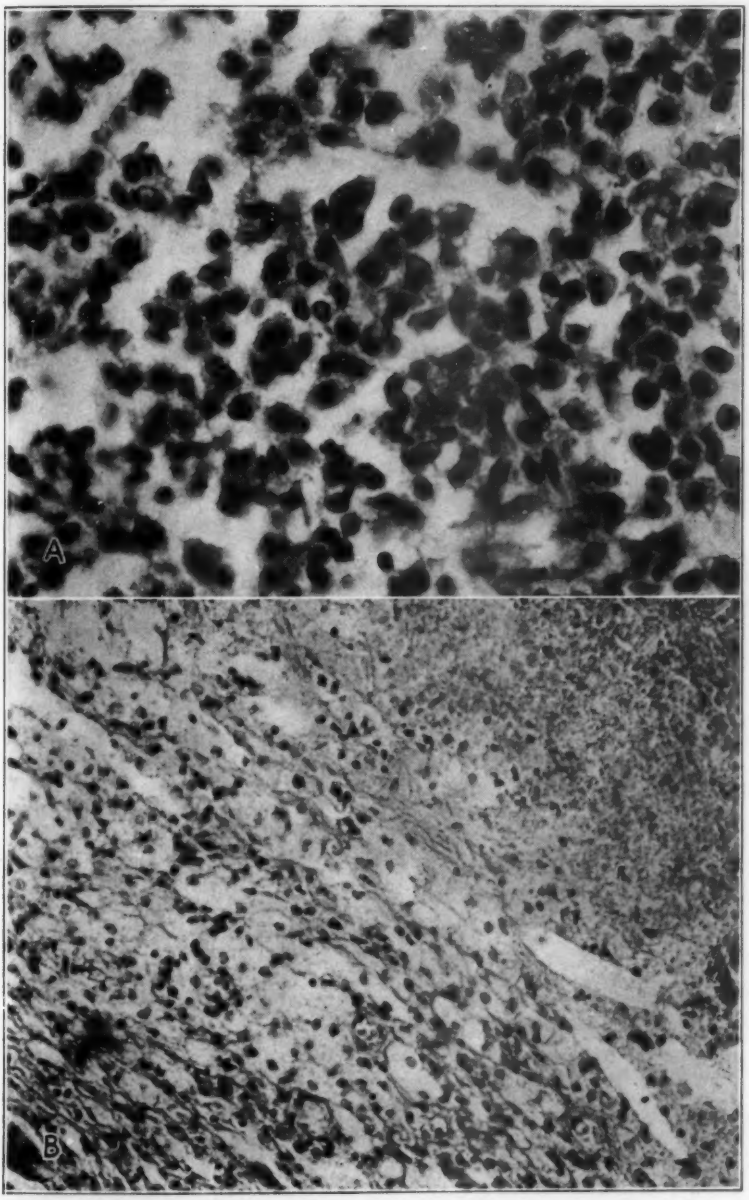

Fig. 4.—Photomicrographs of section of area of destruction from biopsy specimen of rib before death (*A*, × 500) and at autopsy (*B*, × 220).

temporal area through the roof of the orbit. The teeth were loose, and, in the mandible on the right side, a large ulcer with a defect in the bone was present. Throughout the skull were numerous, rounded, tumor-like masses occupying the diploe. Some of these had completely eroded the inner table and were adherent to the dura. Occupying the inner surface of the dura were a number of whitish and

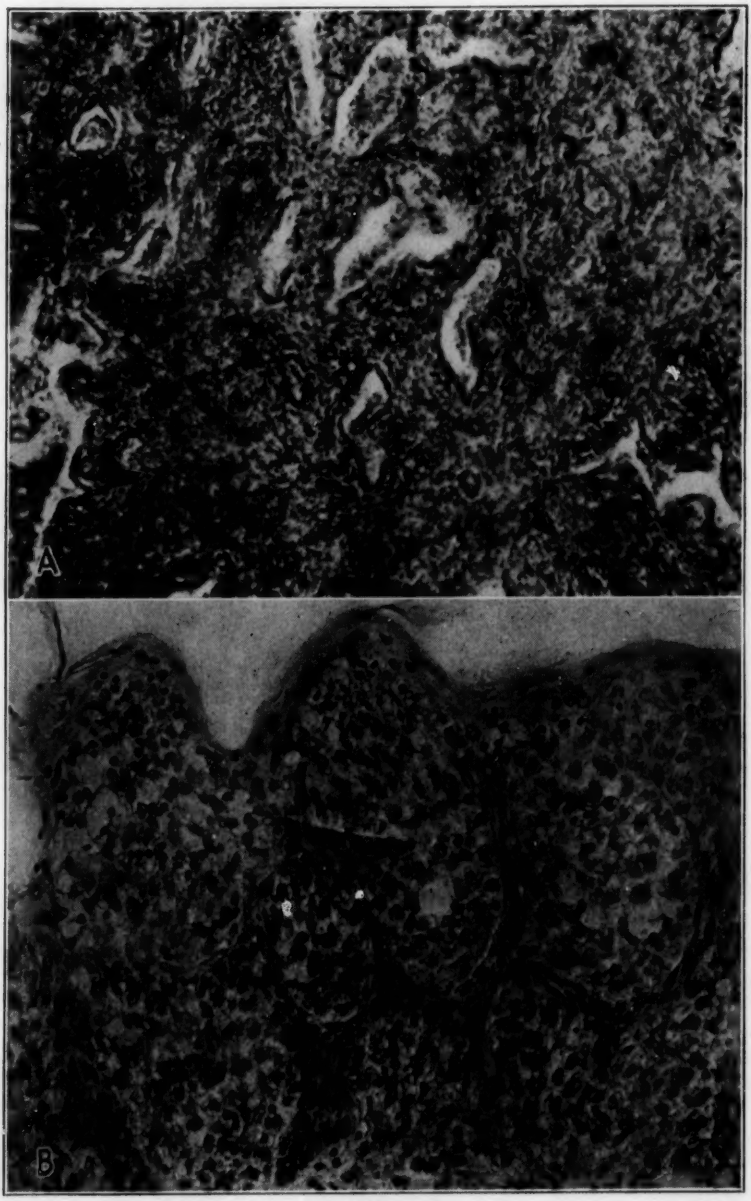

Fig. 5.—Photomicrographs showing interstitial fibrosis of lung (*A*, × 110) and granulomatous foci of the skin (*B*, × 220) at autopsy.

yellowish sessile masses. The petrous portion of the right temporal bone had eroded, with exposure of the middle ear. The brain and the pituitary gland were normal. There were no deposits about the sella turcica. The right fourth rib in its midportion was occupied by a mass of friable, putty-like, yellowish tissue. The bone in this situation was almost completely replaced and could be cut with scissors.

The lungs were similar to each other and presented an unusual appearance. They showed almost complete consolidation and sank in water. On cross section, they cut with considerable resistance and showed only an occasional crepitant area. The parenchyma of the lungs and the pleura exhibited a peculiar mottled pattern, with reddish areas superimposed on a yellow background.

The heart, pancreas, liver, spleen, kidneys and adrenal glands exhibited no relevant gross lesions.

Microscopic Examination.—Sections of rib showed the central portion to be almost completely necrotic (fig. 4*B*). Among the granular debris were many acicular spaces indicating free cholesterol crystals. Numerous macrophages bearing hemosiderin pigment were also present. About the necrotic areas were dense accumulations of foam cells scattered in granulation tissue. At the periphery of the lesion was a dense collagenous fibrous tissue containing groups of foam cells. Sections of dura showed an essentially similar picture. Sections of lung showed a most unusual degree of interstitial fibrosis, with a tremendous reduction in the number of alveolar spaces (fig. 5*A*).

The small number of persisting alveoli were lined with cuboidal epithelium; many contained pus cells. There was a diffuse increase in interstitial connective tissue which was particularly rich in capillaries. Scattered throughout the fibrous tissue were numbers of macrophages, some of which had been converted into foam cells. Sections stained for fat showed tremendous deposits of fatty droplets throughout this scar tissue. Sections of spleen showed a few small granulomatous foci in the malpighian bodies, which were similar to those seen in the spleen in the first case. The skin showed peculiar, patchy, subepidermal foci of a granulomatous type (fig. 5*B*). The predominating cell was the macrophage. The inflammatory infiltration in several places was involving the epidermis, and in other situations the epidermis was replaced by it. Sections of liver, pancreas, adrenal glands, kidney, heart and vertebral bone marrow showed nothing significant.

COMMENT

In the original descriptions of Hand-Schüller-Christian disease, emphasis was laid particularly on the clinical and roentgenologic observations, rather than on the more fundamental anatomic basis. Accordingly, the exophthalmos, diabetes insipidus and the defects in the membranous bones were universally mentioned as the essential features. Gradually, with study of increasing numbers of cases it came to be recognized that the clinical features in any given case depended solely on the localization of the xanthomatous deposits. Thus, increasing numbers of cases were diagnosed, and the clinical conception of the condition became wider and wider. However, it was emphasized consistently that the histologic criterion necessary for anatomic diagnosis was the presence of foam cells in cholesterol-containing granulomas.

With this strict criterion in mind, a number of cases showing reticuloendothelial granulomas were described.[7] The authors considered these conditions to be entities distinct from Hand-Schüller-Christian disease and excluded that diagnosis chiefly because of the absence of foam cells from the lesions. Among these conditions may be mentioned: (1) infectious reticuloendotheliosis, (2) Letterer-Siwe disease and (3) solitary or eosinophilic granuloma of bone.

According to the recorded descriptions of the lesions, the histologic changes in so-called infectious reticuloendotheliosis and Letterer-Siwe disease are identical. In the first condition, the authors considered that certain clinical phenomena indicated an infectious origin. This evidence is not convincing, since any infections occurring in the course of the disease might easily be of secondary nature, as in our second case. Wallgren[8] pointed out that both conditions may be classified as nonlipid reticuloendothelioses, and he considered them to be essentially the same condition. Wallgren's cases furnish a definite link between this group of cases and the frank lipid reticuloendotheliosis known as Hand-Schüller-Christian disease. He considered that so-called infectious reticuloendotheliosis, Letterer-Siwe disease and Hand-Schüller-Christian disease are all manifestations of one fundamental disease process. He pointed out that the essential feature of this process is a generalized proliferation of reticuloendothelial cells giving rise to disseminated granulomas. His evidence indicated that if the proliferation occurs in infants or young children the process usually runs a relatively malignant course, with a particular tendency toward hemorrhagic diathesis and the development of progressive anemia. In these cases, the anatomic picture is characterized by a proliferation of reticuloendothelial cells in the bone marrow, lymph nodes, thymus gland, spleen and liver, with a well marked tendency for the development of hemorrhages in the lesions. In some of these cases the phagocytic properties of the macrophages in the granulomas are shown by their ingestion of lipid from the body fluids. In the exceptional cases, particularly those in which necrosis develops, the macrophages may become cholesterol-containing foam cells. In older children, the disease tends to run a more protracted course and the macrophages have sufficient time to ingest a large quantity of cholesterol. In certain places the resulting foam cells may far surpass in numbers the nonlipid-containing macrophages. In some cases, particularly those of adults, the untoward macrophage proliferation ceases; the infiltrates are absorbed; the necrotic areas are replaced with scar tissue, and the disease is cured.

7. (*a*) Lichtenstein, L., and Jaffe, H. L.: Am. J. Path. **16**:595, 1940. (*b*) Abt and Denenholz.[6a] (*c*) Otani and Ehrlich.[6b]

8. Wallgren, A.: Systemic Reticuloendothelial Granuloma: Nonlipoid Reticuloendotheliosis and Schüller-Christian Disease, Am. J. Dis. Child. **60**:471 (Sept.) 1940.

With regard to the recently described bone lesions designated as "solitary granuloma of bone" by Otani and Ehrlich[6b] and "eosinophilic granuloma of bone" by Lichtenstein and Jaffe[7a] it is the opinion of some authors (Farber and Gross[9]) that they represent solitary bone lesions of the Hand-Schüller-Christian variety. Their histologic features conform to the description that was given previously, and, since none of these cases came to autopsy, it is impossible to deny the existence of visceral lesions. It may be that these cases should be considered as exceptional examples of Hand-Schüller-Christian disease, with a single bony lesion and minimal visceral changes.

With this widened conception of the disease in mind, observations on the 2 cases just reported may be presented. The first infant showed a dissemination of reticuloendothelial granulomas which, although showing an occasional fatty droplet, failed to exhibit the characteristics of foam cells and cholesterol crystals. These so-called nonlipid granulomas were widely scattered, involving particularly the bone marrow, lymph nodes and spleen. The replacement of the blood-forming marrow tissue with the granulomas was responsible for the anemia, which was the most conspicuous clinical feature of the case. The tumor-like proliferation of the macrophages was particularly striking in the biopsy specimen from the skull, which showed a considerable number of mitotic figures.

With regard to the second case, the most pronounced changes were present in the lungs, skin, rib and skull. There were only minor infiltrations in the spleen, and the lymph nodes and the vertebral marrow were entirely free of them. The peculiar cutaneous infiltration is described in cases of so-called Letterer-Siwe disease. In the original biopsy specimen from the rib the histologic features were those of a nonlipid granuloma. At the autopsy several months later, sections from the same area showed extensive necrosis with acicular spaces representing cholesterol crystals, and there was a massive infiltration of foam cells. A considerable quantity of hemosiderin pigment was also present, emphasizing the tendency for hemorrhages to occur in the lesions. Some of the well developed lesions in the dura also showed this foam cell picture. On the other hand, the small miliary lesions in the spleen showed none of the tendency to hemorrhage. These observations lend support to the theory that the deposition of cholesterol in the granulomas is a secondary occurrence, unrelated to the original development of the lesions. In the lesion of the rib proliferation of granulation tissue was beginning. An advanced stage of this fibrosing process was present in the lungs, and it is felt that this represents the "healed" stage of the process. In the clinical history it was mentioned that the child exhibited a "troublesome"

9. Farber, S., abstracted, Am. J. Path. **17**:625, 1941. Gross, P., in discussion on Farber.

cough for several months prior to the development of labored breathing. This fact, together with our histologic observations, suggests that the pulmonary changes developed progressively through the stages of nonlipid to lipid granulomas, with the later occurrence of necrosis and eventual organization leading to dense fibrosis. In the earlier stages this case presented the features described in Letterer-Siwe disease, but with full maturation of the lesions the complete picture of Hand-Schüller-Christian disease was evident. This case seems to support Wallgren's contention that the two conditions are essentially the same and represent merely the early and the late stages of one process.

In both cases on the initial examination, there was a moderate degree of leukocytosis and fever. Such evidence was used in the past to bolster the idea of an infectious agent as the responsible factor. This was particularly true of that group of cases which were called infectious reticuloendotheliosis. It occurred to us that the fever and leukocytosis may well be explained on an entirely different basis: namely, that of a nonspecific reaction to the presence of necrotic tissue. As mentioned previously, necrosis was a prominent histologic feature in the granulomatous lesions. This nonspecific reaction may be compared with that developing after a cardiac infarction.

Values for blood cholesterol in most of the recorded cases of this disease were within the normal range of 160 to 220 mg. per hundred cubic centimeters. Occasionally, however, a given case shows hypercholesteremia. In the second case presented, on one occasion a value of 230 mg. was obtained, but at a later date a normal value of 170 mg. per hundred cubic centimeters was recorded. The suggestion is advanced that the hypercholesteremia may be produced by the excessive liberation of cholesterol from the granulomatous lesions as the result of necrosis. It is evident that this liberation occurs because cholesterol crystals are so commonly seen in the necrotic areas. It would appear that necrosis is continually occurring in some of the lesions but that the liberated cholesterol is reabsorbed by other granulomatous areas and no increase is observed in the blood. If, by chance, necrosis developed simultaneously in a large number of lesions, the amount of cholesterol set free might be sufficiently large to produce a transient hypercholesteremia. In support of this view the observation was made that at the time the elevated value of 230 mg. for blood cholesterol was obtained, the temperature was ranging between 99.6 and 104 F. This swinging temperature had been present for ten days previously. Pyrexia in the absence of gross infection suggests that necrosis in the lesions was severe. Conversely, at a time when the temperature was normal or only slightly elevated, one might postulate that necrosis was minimal and that the blood cholesterol should be therefore within normal limits. As a matter of fact, at the time the lower figure of 170 mg. per hundred cubic centimeters was obtained, the tem-

perature for the previous ten days had been at a consistently low level, never rising above 100 F. Furthermore, in the first case only 1 determination of blood cholesterol was made and this yielded the low value of 110 mg. per hundred cubic centimeters. During this period the temperature was in the neighborhood of 99 F.

SUMMARY

1. Two cases of Hand-Schüller-Christian disease are presented, the features of which tend to support the hypothesis that the condition is a systemic reticuloendothelial granuloma of unknown origin.

2. Evidence is produced suggesting that the presence of cholesterol in the lesions is a secondary occurrence resulting from the ingestion of the lipid from the tissue fluids by the macrophages of the preformed granulomas.

3. This theory fits the well recognized fact that the value for serum cholesterol is normal in most cases. With the onset of necrosis in the lesions, this ingested cholesterol is liberated from the cells and is observed lying free in the lesions in crystalline form. From these sites it may be absorbed into the blood stream and give rise to a transient hypercholesteremia.

Christie Street Hospital (4).

TREATMENT OF ANURIA

Management of Patients with Intrarenal Lesions

EDWARD L. PRATT, M.D.
NEW HAVEN, CONN.

FAIRLY SATISFACTORY methods of treatment are available for combating anuria resulting from obstructive and external causes.[1] Therefore the present discussion will be limited to the treatment of those patients with previously adequate renal function in whom anuria developed abruptly as the result of intrarenal lesions. This clinical situation is encountered with increasing frequency because reactions from transfusions of incompatible blood, crush injuries and the intrarenal complications of sulfonamide therapy produce this type of anuria.

As a result of the study of 9 anuric patients, I believe that death from anuria usually is due to the disorganization of the structure of the internal environment and not to the accumulation of urea or hypothetic toxins. Therefore the rational approach is to preserve the normal volume and composition of the body fluids.

In the presence of anuria and in the absence of intake of food and fluids, the volume of body water will be progressively reduced through insensible expenditure by way of the lungs and the skin, and the concentrations of body fluid electrolytes will rise unless, as is occasionally the case, losses occur in vomitus and in diarrheal stools. Owing to consumption of body protein, the quantity of the products of the oxidation of protein in the body fluids will be increased and their concentrations will, therefore, rise more extensively than those of the electrolytes. It is also evident that an intake of protein will add to the accumulation of nitrogenous end products. On the other hand, if one provides a water intake which is larger than the insensible expenditure, the concentrations of the electrolytes will fall below their physiologic values.

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From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals, Boston.

Presented in part at the Sixteenth Annual Meeting of the Society for Pediatric Research, Skytop, Pa., May 1, 1946.

1. Styron, C. W., and Leadbetter, W. F.: The Treatment of Anuria, New England J. Med. **230**:721 (June 15) 1944.

These considerations lead to a simple rationale of treatment. Water should be provided to the extent of replacement of the insensible expenditure, and glucose should be given in sufficient quantity to obtain maximal sparing of body protein. If the concentrations of the large components of the extracellular electrolyte structure have been lowered by losses from the gastrointestinal tract or, in hot weather, from the skin, they should be rebuilt by the provision of appropriate quantities of sodium chloride and sodium bicarbonate. If elevated concentrations are found, a deficit of water is indicated, which should be repaired. This plan of treatment may be expected in most instances to extend survival until spontaneous recovery of renal function occurs. This rationale has a large importance because of the almost regular failure of the various procedures which are supposed to induce renal activity. The guiding data required are daily measurements of body weight and less frequent determinations of the concentrations of sodium, chloride and bicarbonate in the serum.

PRELIMINARY STEPS

Once the diagnosis of anuria has been made, the appropriate steps should be taken to determine rapidly whether the cause is obstruction of the urinary tract, extrarenal factors diminishing the effective glomerular filtration pressure or an intrarenal disturbance. These steps include: a history, physical examination and a flat roentgenogram of the abdomen. The history should elicit information regarding: (*a*) condition predisposing to obstructive or circulatory disorders, (*b*) the use of agents which may have injured the kidneys and (*c*) a detailed estimation of the intake and outgo of fluids and electrolytes in the preceding twenty-four to forty-eight hours. Often catheterization of the bladder is desirable, and in some instances it may be necessary to catheterize the ureters to determine whether an obstruction is present which can be relieved by lavage, instrumentation or other surgical procedure. During this initial examination an accurate measurement of body weight should be made and a sample of blood drawn for immediate determination of concentrations of bicarbonate, chloride and sodium in the serum. Determinations of other substances in the blood, such as urea, nonprotein nitrogen, potassium, phosphorus or creatinine, while of interest, are not necessary for this plan of management.

The body weight and the electrolyte concentrations, evaluated in the light of the history, are used to estimate whether a deficit or excess of body water exists and whether the relations of the major extracellular ions are altered. Until one has some knowledge of the direction and the magnitude of the derangement already present in the body fluids, the patient should receive nothing orally or parenterally, lest inappropriate, unguided treatment aggravate the existing disturbance.

PLAN OF MANAGEMENT

As soon as the diagnosis of an intrarenal type of anuria has been made, the following program should be instituted:

1. An initial definition of the electrolyte structure should be made from measurements of the serum sodium, chloride and bicarbonate.

2. Sufficient fluids should be allowed each day to keep the body weight constant. This allowance will average only 30 to 60 cc. per kilogram per twenty-four hours for infants, and even smaller amounts per kilogram will be sufficient for older children and adults. This allowance of water to replace imperceptible losses is modified above or below the figure given as indicated by the serum concentration of sodium; an elevation in sodium concentration demands replenishment of water deficit in addition to provision of water for insensible expenditure, whereas a lowered concentration indicates limitation of water intake until the normal value for sodium has been roughly restored.

3. In the event of reduction in the concentrations of the serum electrolytes, appropriate amounts of sodium, chloride and bicarbonate should be administered to restore the serum concentrations of each to satisfactory values. The amounts, in milliequivalents, will equal approximately the estimated extracellular fluid volume in liters multiplied by the deficit in milliequivalents per liter.

TABLE 1.—*Electrolyte Structure for 6 Anuric Patients on Admission to the Hospital*

Patient	Duration of Anuria, Days	Initial Concentrations in Serum				Non-protein Nitrogen, Mg./100 Cc.
		Sodium, mEq./L.	Chloride, mEq./L.	Bicarbonate, mEq./L.	Potassium mEq./L.	
Z.	3	108	67	20.6	7.6	63
R.	4½	122	83	14.6	5.8	137
B.	4	133	80	25.0	3.8	133
Pi.	2½	134	102	10.2	9.8	75
Pn.	¾	136	92	20.0	4.1	41
K.	3	160	119	14.3	7.3	185

4. The only food substance required is glucose, of which enough should be provided to furnish infants 30 to 60 calories per kilogram of body weight per day. To older children and adults 100 to 200 Gm. of glucose per day, irrespective of body weight, is administered. The glucose can generally be given by mouth.

5. The therapy should be guided by frequent repetition of relevant laboratory determinations.

ILLUSTRATION

The need for laboratory measurements to describe the electrolyte structure on the patient's admission to the hospital is demonstrated by the initial values for serum chloride, sodium and bicarbonate for 6 anuric patients shown in table 1. Concentrations of serum sodium ranged from 108 to 160 milliequivalents per liter and those of serum chloride from 67 to 119 milliequivalents per liter. Despite these great variations, competent clinical appraisal of the patients failed to provide any reliable clues to either the direction or the magnitude of these changes in any

patient except 1 who displayed signs of "water intoxication." The changes in the serum and the duration of anuria have little relation. As shown in table 1, the electrolyte concentrations are so variable that therapy cannot be started without quantitative measurements.

Control of the volume of body fluids and maintenance of extracellular electrolyte concentrations are illustrated by the course of illness in the following infant who was anuric for at least eleven days.

Mc., one of twin girls, was born on May 20, 1944, weighing 1,361 Gm. In August of that year she was admitted to the Infants' Hospital because of bronchopneumonia. She received sulfathiazole for four days without untoward symptoms. Several urinalyses were made, and all results were normal. The highest specific gravity of the urine recorded was 1.026. Her height was below the 3 percentile rank; her weight was at the 5 percentile rank.

After discharge from the hospital she had several mild infections of the respiratory tract. She was brought to the outpatient department on March 13, 1945 because of a "cold" for one week and diarrhea for two days. The infant was said not to have voided in the previous twenty-four hours but did so during examination. The analysis of this specimen revealed nothing abnormal. Naphazoline ("privine") hydrochloride nose drops prescribed at this visit was the only medicament received, according to the informant. In the evening of the same day the patient returned, and myringotomy was performed bilaterally, releasing purulent material from which Staphylococcus aureus, Hemophilus influenzae and an alpha streptococcus were cultured.

Because of irritability and persistence of fever the patient was admitted to the Infants' Hospital on the evening of March 14. Except that the parents were not certain that the patient had voided in the past twenty-four hours, no additional relevant information was obtained from the history and physical examination. The infant appeared only slightly ill, and no alteration in hydration was clinically evident.

During the first twelve hours the patient received three doses of sulfadiazine sodium U.S.P. subcutaneously, a total of 0.9 Gm., and ingested 100 cc. of milk, 1 Gm. of potassium citrate and 0.5 Gm. of sodium bicarbonate. A hypodermoclysis of 250 cc. of a mixture of equal parts of isotonic solution of sodium chloride and 5 per cent dextrose solution in water was given shortly after her admission. During this period the patient vomited a small amount once and passed no urine.

As soon as it was apparent that anuria existed, sulfonamide therapy was stopped; only glucose in distilled water was given orally. A detailed record of all intake and output was kept, and each day accurate measurements of body weight were made. In addition, frequent determinations of certain constituents of the blood or serum were performed. A partial list of the values obtained at various intervals, considering the day of admission as the first day in the hospital, are recorded in table 2.

The patient passed no urine for eleven days, and an output sufficient to produce a lowering of the nonprotein nitrogen level in the blood did not occur until the fifteenth day. In an attempt to promote the formation of urine, the following steps were taken: 35 cc. of 50 per cent dextrose solution was given intravenously on two occasions; 18 cc. of 5 per cent saline solution was injected intravenously twice; spinal anesthesia was induced on the fifth day; each ureter was catheterized and lavaged on the sixth day, and a decapsulation of the right kidney with insertion of a nephrostomy tube was performed on the seventh day. All these pro-

cedures were ineffective. However, a small biopsy specimen from the right kidney was obtained. The section revealed small areas of infarction, with necrosis in the infarcted areas. Elsewhere, there were changes in many of the glomeruli, proximal convoluted tubules and arterioles. Many glomeruli showed focal areas of endothelial proliferation and small fibrin thrombi in a number of glomerular tufts. The epithelium lining the proximal convoluted tubules was dark staining and markedly flattened. The tubules contained large amounts of bright esoinophilic debris. A bluish staining, highly refractile mass, probably representing a crystal, was seen in one dilated tubule. The walls of the arterioles and small arteries in the noninfarcted areas were greatly thickened, and a number of small vessels contained minute fibrin thrombi. No significant inflammatory reaction was present in the section.[2]

The amounts and significance of the water and electrolytes given during the first two weeks will be discussed later. The patient voided a few cubic centimeters of urine on the eleventh day and gradually attained a normal output. The blood nonprotein nitrogen level fell to 41 mg. per hundred cubic centimeters on the twenty-seventh day, but it subsequently rose to about 60 mg. per hundred cubic

TABLE 2.—*Results of Laboratory Tests*

Day in the Hospital	Electrolyte Concentrations in the Serum					Nonprotein Nitrogen, Mg./100 Cc.	Free Sulfadiazine, Mg./100 Cc.	Miscellaneous, Mg./100 Cc.
	Sodium, mEq./L.	Chloride, mEq./L.	Potassium, mEq./L.	Bicarbonate, mEq./L.	Protein, Gm./100 Cc.			
2	128	97	—	—	—	104	16	—
3	140	105	8.9	—	5.8	104	14	Calcium=9.1 Phosphate=10.9
5	143	102	6.9	—	—	—	—	—
7	139	105	—	—	5.2	—	6.1	—
9	142	103	4.4	12.6	—	150	5.6	Total sulfadiazine=8.6
13	152	—	3.7	15.9	6.2	175	—	Phosphate=7.4
20	143	105	3.0	18.5	6.4	133	1.4	—
28	145	106	6.3	—	5.6	48	—	—

centimeters, where it has remained for the past year and a half. Values for urea clearance on the fifty-first day and again seven months later were about 40 per cent of normal. The child was seen on numerous occasions and made fairly satisfactory progress, in spite of her poor renal function and repeated infections of the upper respiratory tract. Growth was moderately retarded, her body weight at 2 2/3 years of age being only 9.1 Kg.

Regulation of Body Fluids.—Daily measurements of body weight allow one to control the volume of total body fluids. Chart 1 depicts the relation between fluid intake and body weight during the eleven days of anuria in the patient just described. Extrarenal losses of fluid averaged about 300 cc. per twenty-four hours as evidenced by a gain in weight when larger quantities of fluid were given, for example, on days 5, 7 and

2. The surgical procedures were performed by Dr. Orvar Swenson. The biopsy of the kidney was described by Dr. J. B. Arey and supplied by the Department of Pathology.

8, or by a loss of weight when smaller quantities were administered, as on days 9 and 10. Hence, the volume of body fluids may be kept approximately constant by giving the appropriate amount of fluid to keep body weight stationary.

Regulation of Extracellular Fluid Electrolytes.—Keeping the concentrations of the extracellular fluid electrolytes on the mark is more com-

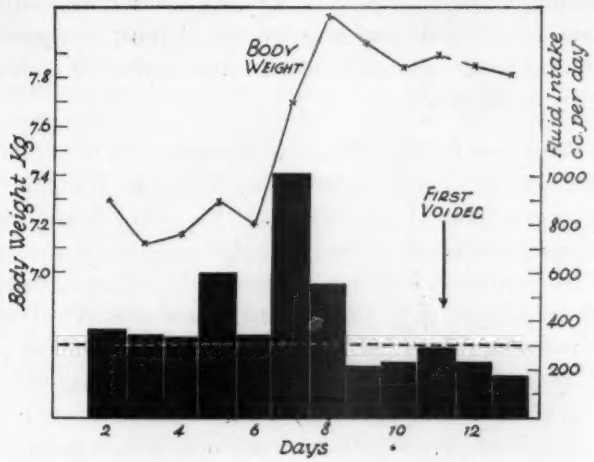

Chart 1.—The relation between fluid intake and body weight of patient Me. during the eleven days of anuria.

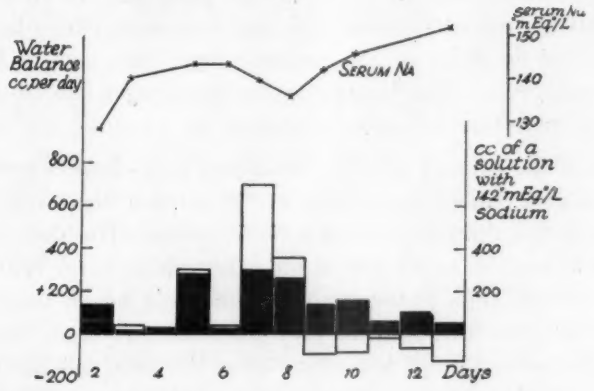

Chart 2.—Influence of water balance and sodium intake on the concentration of sodium in the serum.

plicated because the concentration of each component depends on two variables: first, the change in the volume of the body fluids and second, the gain or loss of the element. The manner in which the concentration of serum sodium is influenced by these two variables is shown in chart 2. For example, the serum sodium may be raised either by decreasing

the volume of the body fluids (days 9 and 10) or by administering relatively more sodium than water (day 2). The addition of water to the body fluids with comparatively smaller amounts of sodium will result in a fall in the serum sodium concentration, as shown on days 7 and 8. Therefore, in order to maintain the proper relation between the volume of body fluid and the electrolyte concentration, it is essential to gage the amount of each electrolyte to be administered from the changes in body weight and the results of fairly frequent laboratory measurements of the levels of serum sodium, chloride and bicarbonate. It must be appreciated that each anion and cation should be dealt with separately as long as renal adjustment is in abeyance.

Serum Potassium Levels.—Since the consumption of body protein and glycogen is known to liberate intracellular potassium, it might be expected that the concentration of potassium in the serum would rise to toxic levels. Hoff and associates[3] showed that in experimental anuria the serum potassium concentration does rise progressively and eventually reaches a lethal level; it is apparently the limiting factor in survival. Fortunately, the serum potassium level did not increase in our patients, perhaps because body protein and glycogen were extensively protected by providing an intake of glucose. During the long period of complete anuria in the previously described patient, the concentration of potassium in the serum decreased from 8.9 milliequivalents per liter on the third day to 3.8 on the tenth day. In another patient 16 months of age, who was managed according to the outlined plan, the serum potassium fell from 5.8 to 2.7 milliequivalents per liter during eighteen days of extreme oliguria. During this period the daily output of urine ranged from zero to 135 cc. and averaged only 40 cc. The blood nonprotein nitrogen level rose from 28 to 170 mg. per hundred cubic centimeters.

Although the values for serum potassium were often dangerously high at the time of a patient's admission to the hospital, the levels slowly and progressively fell during the course of treatment. The decrease may be explained in part by expansion of the extracellular fluid volume and by the losses of potassium in sweat and in the stools, which were frequently loose. Perhaps the formation of glycogen from the sugar fed these patients also removed some potassium from the extracellular fluid, since an increase in the glycogen stores would involve intracellular storage of potassium.

"Forcing" Fluids.—All too frequently it is advised that large quantities of water or glucose solutions be administered to anuric patients. The inadvisability of such therapy is illustrated by the course of illness in an-

3. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: The Cause of Death in Experimental Anuria, J. Clin. Investigation **20**:607 (Nov.) 1941.

other patient with anuria following the administration of sulfadiazine. He was not treated according to the concepts presented; rather, the experiences with this patient led, in part, to the development of the present plan of therapy.

M. Z., an 18 month old boy, was given 3 Gm. of sulfadiazine per day for three and a half days because of an infection of the respiratory tract with fever. His symptoms were relieved, but anuria developed abruptly on the fourth day. For three days at home fluids were "forced." Sips of water were urged repeatedly, and frequent rectal taps were given and retained. On the third day of this regimen the patient became drowsy and had muscular twitchings; then he had a generalized convulsion, after which he was admitted to the Infants' Hospital. Physical examination revealed an alert, well hydrated, but not edematous, infant with injection of the rhinopharynx, enlarged cervical lymph nodes and severe costovertebral tenderness. No abnormal neurologic signs were present. The blood pressure was normal. After his admission, 750 cc. of water in the form of dextrose solution was administered parenterally. About five hours later the patient became comatose, had generalized convulsions and shallow respirations and repeatedly vomited blood-tinged material. The diagnoses of uremia and so-called water intoxication were considered, and immediate laboratory measurements were undertaken. The serum sodium, chloride and bicarbonate values were 108, 67 and 20.6 milliequivalents per liter, respectively. Samples taken at the same time revealed the serum proteins to measure 6.2 Gm., the nonprotein nitrogen, 64 mg. and the sulfadiazine level, 5.1 mg. per hundred cubic centimeters. As soon as hypotonicity of the body fluids was demonstrated, restoration of the normal ionic concentration was undertaken by intravenous infusion of a 1.8 per cent solution of sodium chloride. Spontaneous recovery of renal function occurred, however, after only one infusion of 100 cc. and before there was appreciable repair of the hypotonicity. The subsequent course of the patient's illness was uneventful. His weight fell from 11.5 Kg. at the time his symptoms were more pronounced to a plateau of 10 Kg. for the period from the fourth to the tenth day in the hospital.

Chart 3 portrays the estimated expansion of the volume of the body fluids resulting from the excessive administration of water to this patient. The volume was derived from a calculation of the concentration of solutes in the extracellular fluid with the assumption that the total solutes in the body remained unchanged. The figure for concentration was based on the measurements of sodium, potassium and nonprotein nitrogen. Then, since the total solutes equals volume times concentration for a normal child weighing 10 Kg., which was the weight of this patient, the total solutes would be 2.17 osmols. Therefore, the volume of the body fluids in the patient at the time of his water intoxication was approximately 2.17 osmols divided by 0.248 osmols per liter, or 8.75 liters. This value corresponds to an addition of 25 per cent of his normal body fluid volume. The data from this patient make emphatically clear the dangerous situation that results when water is given beyond the fixed rate of removal by insensible expenditure. Restoration of normal body fluid tonicity requires the infusion of a hypertonic solution of extracellular electrolyte (sodium chloride), and this involves additional extension of the already expanded volume of extracellular fluid. It is to be noted that the

concentration of protein in the serum, 6.2 Gm. per hundred cubic centimeters, did not reveal the presence of hypotonicity of the body fluids. These values illustrate the fact that serum protein concentration does not reliably reflect electrolyte concentration.

Management Following Anuria.—Generally, when formation of urine commences after a period of anuria, the amount rapidly increases to abnormally large volumes. From the few measurements I have made, it would appear that these urines are dilute, having an osmolar concentra-

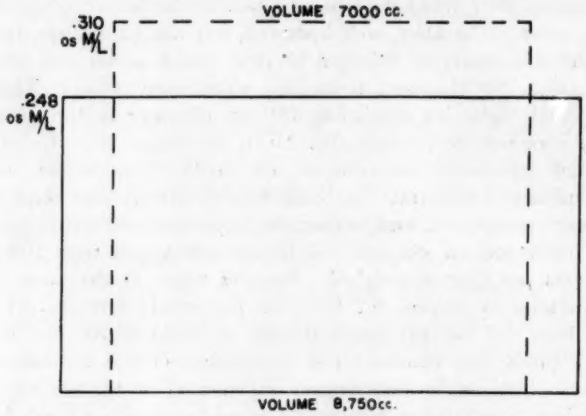

Chart 3.—The estimated expansion of the volume of body fluids in patient M. Z. caused by the excessive administration of water. The expansion is calculated as follows:

In a normal child weighing 10 Kg. there is 7,000 cc. of body fluid. Since total solutes equals the volume times the concentration, or

$$\text{volume} = \frac{\text{solutes}}{\text{concentration}}$$

total solutes in this child = 0.310 osmols × 7,000 cc. = 2.17 osmols. Since the concentration of solutes decreased to 0.248 osmols while the value for total solutes remained the same, the expanded volume $= \frac{217}{0.248} = 8{,}750$ cc. or 25 per cent increase in body fluid.

tion close to that of an ultrafiltrate of plasma and containing only small amounts of sodium and chloride. The cause of this anomalous behavior of the kidneys is not clear. However, characteristic clinical symptoms and serious alterations in the extracellular fluid electrolytes during this period, were described by Luetscher and Blackman.[4] They noted signs of injury to the central nervous system and extreme elevations in the concentrations of sodium and chloride in the serum. Since the latter condition may be fatal, it is important to minimize the alterations in the body fluids

4. Luetscher, J. A., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. **18**:741 (May) 1943.

by not giving excessive amounts of sodium and chloride during the anuric phase and by sharply limiting the administration of electrolytes, while increasing the intake of water, preferably by mouth, once production of urine is reestablished.

COMMENT

The basic assumption that death from anuria results from the disorganization of the structure of the internal environment has not been proved. However, the theory is in accord with many investigations concerning acute renal insufficiency and with the conclusions reached by Bradley in a recent review of this subject.[5] The treatment is essentially the same as that recently reported to be successful by Muirhead and Fromm.[5a]

The practicability and the efficacy of the plan outlined in this paper are demonstrated by the fact that 1 patient survived at least eleven days of complete anuria; another patient was maintained for eighteen days, during which time the volume of urine averaged only 40 cc. per day, and 5 additional patients survived anuria of one to four days' duration. Of the 9 patients, only 2 died. In both these patients irreversible renal lesions were observed at autopsy. One was the previously mentioned patient with severe oliguria. He had polycystic renal disease which had necessitated the removal of his right kidney with its atretic ureter at 1 month of age. Fifteen months later, because of obstruction to the left ureter with hydronephrosis and pyelonephritis, pyelostomy (left kidney) was done. After injection of a solution of 12 per cent sodium iodide into the renal pelvis, oliguria developed. After eighteen days, increasing amounts of urine were produced, up to 300 cc. on the twenty-third day. The patient died of respiratory failure twenty-two days later. A few days prior to death the serum electrolytes were relatively normal. The nonprotein nitrogen concentration was 125 mg. per hundred cubic centimeters, which was the level maintained for the previous ten days. The second death occurred in a 13 day old infant in whom diarrhea and fever developed after circumcision on the sixth day of life. On his admission to the hospital four days later, the patient had Escherichia coli bacteremia, anuria and severe acidosis. He died on the third day in the hospital. Postmortem examination of the kidneys revealed thrombosis of the intrarenal veins.

The amount of glucose recommended in the present study for anuric patients was chosen with the intention of achieving the maximal sparing of protein. It was observed that 100 Gm. of glucose performed this func-

5. Bradley, S. E.: Biochemical Abnormalities During Renal Insufficiency, New England J. Med. **235**:755 (Nov. 21); 791 (Nov. 28) 1946.

5a. Muirhead, E. E., and Fromm, C. S.: Severe Acute Renal Insufficiency with Recovery, J.A.M.A. **137**:1378 (Aug. 14) 1948.

tion in healthy adults.[6] No information was available for determining the requirement in infants, although the amount probably is proportional to metabolic rate rather than to weight. Kloff expressed the opinion that the greatest sparing of protein can be attained through giving carbohydrate and fat in amounts to cover the total caloric expenditure[7]. More data are necessary to decide this point. Apparently, neither the smaller amounts I prescribed nor the full coverage of caloric expenditure practiced by Kloff has been harmful.

Although the present report is based on the study of infants and children, the same principles can be applied to the management of adults by taking into account the differences in size and rate of metabolism.

Recently, the literature on the removal of abnormal accumulations of metabolic products by dialysis, utilizing either an artificial membrane[8] or the peritoneum,[9]was reviewed.[10] These reports demonstrate that large amounts of urea can be removed. These methods can be used to adjust the electrolyte concentrations in the extracellular fluid, provided rapidly completed measurements of the levels in the serum are carried out repeatedly.[11] That extensive and serious alterations in the composition of the fluids within the cells may be produced by dialysis should be kept in mind. At present, it would seem that in most instances any substitute for the kidney involves risk to the patient and provides no more certain preservation of the integrity of the body fluids than that obtainable with the principles discussed in this report. Certain patients, those inappropriately treated prior to admission or those with complications, such as febrile illnesses, trauma or very recent operations, may have such extensive abnormalities in the body fluids, especially elevated serum potassium levels, that one of the dialyzing methods should be used in order to readjust the composition of the body fluids. This state could then be held by following the plan already presented.

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6. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus, ed. 5, Cambridge, Mass., Harvard University Press, 1947, chart 47.

7. Kolff, W. J.: New Ways of Treating Uraemia: The Artificial Kidney, Peritoneal Lavage, Intestinal Lavage, ed. 1, London. J. & A. Churchill, Ltd. 1947.

8. Abel, J. J.; Rowntree, L. G., and Turner, B. B.: On Removal of Diffusible Substances from Circulating Blood of Living Animals by Dialysis, J. Pharmacol. & Exper. Therap. **5**:257 (Jan.) 1914.

9. Ganter, G. Ueber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse, München. med. Wchnschr. **70**:1478 (Dec. 14) 1923.

10. Hoff, H. E.: Medical Progress: Physiology, New England J. Med. **235**: 885 (Dec. 12) 1946. Kolff[7].

11. Abbott, W. E., and Shea, P.: Treatment of Temporary Renal Insufficiency (Uremia) by Peritoneal Lavage, Am. J. M. Sc. **211**:312 (March) 1946.

CONCLUSIONS

A practical plan of management for patients with anuria due to intrarenal derangements of transitory nature is described. Only relatively simple measurements, which can be carried out in most hospital laboratories, are required.

The basic principle is the preservation of the normal volume and composition of the body fluids. This can be accomplished, in most instances, by regulating the intake of fluids and electrolytes according to daily measurements of body weight and less frequent determinations of the concentration of serum sodium, chloride and bicarbonate. The report of the case of an infant who was anuric for eleven days is given to illustrate these principles.

The danger of administering large amounts of fluids is emphasized by data from another patient.

The efficacy of this plan is demonstrated by the fact that all 7 anuric patients with a reversible renal lesion survived. Two other patients died, and each was shown at autopsy to have irreversible renal damage.

789 Howard Avenue (4).

TREATMENT OF EXOPHTHALMIC GOITER IN CHILDHOOD

A Report of a Follow-up Study in Twelve Cases

ANNE TOPPER, M.D.
NEW YORK

THAT THE MOST efficacious method of managing exophthalmic goiter in childhood still remains debatable is evidenced by a review of the literature. Opinions vary from those favoring immediate surgical treatment in all cases[1] to those advocating only medical management.[2] Still others believe that radiation procedures produce as good results as surgical intervention.[3]

As to roentgen ray therapy, there is nothing conclusive in the literature to indicate its importance in childhood. One is naturally wary of its use in growing children and young adolescents.

From the Pediatric Service of Dr. Murray H. Bass, Mount Sinai Hospital.

1. Helmhoz, H. F.: Exophthalmic Goiter in Childhood, J. A. M. A. **87**:157 (July 17) 1926. Richter, H. M.: Am. J. Surg. **9**:115, 1930. Green, E. I., and Mara, J. M.: Surg. Gynes. & Obst. **53**:375, 1931. Dinsmore, H. S.: Hyperthyroidism in Children: Review of Fifty-Seven Cases, J. A. M. A. **99**:636 (Aug. 20) 1922. Crile, G., and others: Diagnosis and Treatment of Diseases of the Thyroid Gland, edited by Amy F. Rowland, Philadelphia, W. B. Saunders Company, 1932. Abbot, A. C.: Internat. Clin. **4**:98, 1932. Lehman, J. A.: West. J. Surg. **44**:528, 1936. Beilby, G. E., and McClintock, J.: New York State J. Med. **37**:563, 1937. Welti, H.: Mem. Acad. de chir. **63**:1229, 1937. Gould, E. P., and Robertson, J. D.: Brit. J. Surg. **25**:700, 1938. Klapper, H.: Internat. Clin. **2**:234, 1939. McKnight, R. B.: J. South Carolina M. A. **35**:168, 1939. Black, J. B., and Webster, B.: J. Clin. Endocrinol. **1**:839, 1941.

2. Bloom, C. J.: South. M. J. **28**:123, 1935. Bram, I.: Arch. Pediat. **54**:419, 1937. Atkinson, F. R.: Brit. J. Child. Dis. **35**:165, 1938. Redich, W., and Perloff, M. H.: Endocrinology **26**:221, 1940. Reilly, W. A.: Thyrotoxicosis, Am. J. Dis. Child **60**:79 (July) 1940. McIntosh, C. B.: J. Pediat. **25**:133, 1944. Burke, F. G.: M. Ann. District of Columbia **14**:108, 1945. Bram, I.: New York State J. Med. **45**:1543, 1945.

3. Jenkinson, L. J.: Radiology **6**:380, 1926. Manville, L. J.: ibid. **18**:568, 1932. Coulton, P., and Wert, W. L.: Lancet **2**:535, 1934. Rose, E.: Rose, E. K., and Pendergrass, E. P.: J. Pediat. **7**:325, 1935. Harris, J. H., and Rose, E.: Am. J. Roentgenol. **36**:610, 1936. Pfahler, G. E., and Vastine, I. H.: Radiology **34**:43, 1940. Soley, M. H., and Stone, R. S.: Roentgen Ray Treatment of Hyperthyroidism, Arch. Int. Med. **70**:1002 (Dec.) 1942. Hertz, S., and Roberts, A.: West. J. Surg. **54**:474, 1946. Chapman, E. M., and Evans, R. D.: Treatment of Hyperthyroidism with Radioactive Iodine, J. A. M. A. **131**:86 (May 11) 1946.

Those in favor of operation have advanced the following arguments:

1. Psychic maladjustment may occur incident to the enforced invalidism of prolonged nonoperative treatment. Because of extended periods of absence from school and play, the child cannot keep pace with his comrades, and thus serious behavior problems may develop.

2. The maintenance of a prolonged state of subacute hyperthyroidism may militate against normal growth and development. Calcium and phosphorus studies and roentgenograms have shown demineralization of the skeleton in some cases. Delay or cessation of maturation has been known to occur, since thyrotoxicosis tends to suppress ovarian function.

3. Latent diabetes may become clinically active as a result of prolonged hyperthyroidism.

4. Medical management means prolonged medical costs.

Those who advocate medical management call attention to these facts:

1. Operative mortality, although concededly low, is ever present.

2. Postoperative complications and sequelae are frequent in childhood. These include postoperative toxicity, tetany, recurrent laryngeal paralysis and keloid scar formation.

Postoperative hypothyroidism, although easily controlled, may exact a greater penalty in the growing child than in the adult.

4. Permanent cardiac damage as a result of prolonged hyperthyroidism is notably rare in childhood.

5. Since the thyroid gland is not the primary pathologic factor, its removal does not eliminate the cause. Postoperative recurrence and persistence of hyperthyroidism are fairly frequent, especially in children.

Before evaluating the results of medical procedures in exophthalmic goiter, one should bear in mind that there may be spontaneous remissions or cessation during the natural course of the disease.

Again, even though the immediate advantages of surgery have been convincingly demonstrated, one must await the late results, when such an important endocrine gland is removed before puberty. Such questions arise as "Will the child grow and mature normally?" "Will the remaining thyroid tissue be sufficient to meet the future needs of the growing organism?"

Follow-up studies made on children with exophthalmic goiter are always helpful in answering such questions, whether these studies are made on large numbers from goiter clinics[4] or in a few selected cases.[5]

4. Kennedy, R. L. J.: Surgical and Medical Treatment of Exophthalmic Goiter of Children: Late Results, Am. J. Dis. Child. **60**:677 (Sept.) 1940.

5. Nixon, N.: J. Pediat. **14**:71, 1941.

The present study was undertaken to evaluate the late results of the management of exophthalmic goiter in 12 children. Eleven of these were admitted to the wards of the Mount Sinai Hospital with this diagnosis during the past twenty-five years; one child was treated at home.[6]

In this group there are 7 girls and 5 boys. The ages on admission ranged from 3½ to 12 years. The duration of the follow-up period is

Fig. 1 (case 1).—A. K., aged 5, during a period of remission.

from three and one half to twenty-five years. One child (case 2) was lost track of after three and one half years. One child died from an apparently unrelated cause (case 5); the rest are still under observation.

6. This case is included through the courtesy of Dr. Murray H. Bass.

REPORT OF CASES

Case 1.[7]—A. K. was first admitted to the hospital on Nov. 1, 1921, at the age of 3½ years. Ketosis and coma had occurred following an exciting boat ride the previous day. The child responded to the administration of dextrose intravenously, and was discharged after two weeks. One month after discharge the mother noted prominence of the neck, slightly bulging eyes and excessive appetite. In the succeeding few months the child had three similar attacks of ketosis, evidently brought on by emotional stress, each time responding to the administration of dextrose solution by hypodermoclysis. The exophthalmos became more marked; the pulse rate continuously ranged between 150 and 160, and the gland increased in size. The child was put to bed for weeks at a time, but all symptoms of exophthalmic goiter increased progressively. Operative intervention was advised by the physician in charge but refused by the parents.

Fig. 2 (case 1).—A. K., aged 29.

The child was treated for years, with long periods of rest in bed, iodine and thyroidin. There were occasional periods of remission (fig. 1). The child, however, could not be sent to school until the age of 8 years. She was then placed in a class for childen with cardiac conditions for five years. Menarche was established at the age of 13. At about that time, the symptoms of hyperthyroidism began to disapper, and the child was placed in a regular class at school.

My attention was first called to this patient at the age of 16. At that time she weighed 84 pounds (38.1 Kg.) and was 144 cm. tall. Her pulse rate was 72 per minute; her basal metabolism showed a normal consumption of 1,368 calories. She seemed well physically, but appeared to be shy and introverted. She was

7. This case was observed for many years by Dr. William Rosenson, through whose courtesy it is included in this series.

still in the grade school, having of course fallen far behind in her school work. Eventually she was graduated from high school at the age of 21 years.

I last saw this patient April 14, 1947 at the age of 29½ years (fig. 2). She weighed 112½ pounds (51.3 Kg.); her height was still 144 cm. She had evidently ceased growing at the age of 16 years. Her pulse rate was 64; blood pressure, 110 systolic and 80 diastolic; basal metabolic rate, plus 2 per cent. She was in excellent physical condition. The heart was entirely normal. She seemed less shy than on her previous visit; she seemed happier, too. She now manages her father's meat market. She has a few "girl friends" but no "boy friends."

This case is interesting because of the age at which symptoms of exophthalmic goiter developed. Crile[8] believes that the occurrence of exophthalmic goiter in children under 5 years of age is so rare as to be a medical curiosity. Because of the early age at which symptoms appeared, I believe that an operation should have been performed. This was refused by the parents, however, who, by the way, are proud of and happy with the medical result. They see their only child restored to normal health, but fail to grasp the psychologic implications. They are sorry their daughter is unmarried, but they believe this to be due to social circumstances, rather than to an emotional maladjustment. They refuse to see any connection between the prolonged invalidism and her present virgin state.

Fig. 3 (case 2).—Appearance of D. S. on admission to hospital.

CASE 2.—D. S., a 7 year old girl, was admitted to the hospital on April 29, 1928, with a history of nervousness, profuse sweating and prominence of the eyes for one year. The past history included repeated attacks of tonsillitis. Examination revealed large cryptic tonsils, carious teeth, bilateral sinusitis and a

8. Crile, G., and Crile, G., Jr.: Am. J. Surg. **37**:389, 1937.

temperature of 103 F. In addition, there were tremor of the hands, an enlarged thyroid gland and marked exophthalmos (fig. 3). The blood pressure was 124 systolic and 70 diastolic; the pulse rate was 120; the basal metabolic rate, plus 30 per cent. The electrocardiogram showed a sinus tachycardia. Low R waves and inverted T waves were present in lead 3.

Treatment consisted of rest in bed and administration of strong solution of iodine in addition to a high caloric diet. The child responded satisfactorily. After three and one half months she was discharged. She had gained 7 pounds (3.2 Kg.). On discharge, her pulse rate was 90 and her blood pressure, 120 systolic and 84 diastolic; the basal metabolic rate was 15 per cent.

The child was followed for the succeeding three and one half years. She did well at school. She had no symptoms of hyperthyroidism other than "slight nervousness." Her last metabolic rate was plus 11 per cent.

Three and one-half years after discharge from the hospital the family moved without leaving an address. It is particularly unfortunate that this child was lost from observation before puberty was established. All symptoms of exophthalmic goiter were pronounced on admission. The immediate response to conservative treatment was excellent and lasted at least three and one half years. However, it is impossible to tell whether the gland was equal to the taxing demands of maturation, or whether, as is more probable, puberty had a permanently beneficial effect.

Case 3.—M. J. F. was first seen in the outpatient department on Sept. 30. 1940, at the age of 7 years. At that time, he presented a history of tremor, irritability and fulness of the neck of six months' duration. His pulse rate was 120; the basal metabolic rate was plus 21 per cent. The family history was very bad. The child had been brought up in an institution since the age of 2 months. The mother, a low grade moron, was confined at the Rockland State Hospital. One other sibling was schizophrenic. Both childen had been born out of wedlock.

The patient was observed in the clinic at intervals for about one and a half years. The symptoms of hyperthyroidism remained subacute for about a year, and then, in spite of rest in bed and sedatives, they became more marked. The child was admitted to the ward May 4, 1942.

Examination on admission revealed a loud blowing systolic cardiac murmur. The pulse rate was 120; the blood pressure, 126 systolic and 70 diastolic; the basal metabolic rate was plus 25 per cent. Fluoroscopy showed slight cardiac enlargement to the left. The cholesterol content was 190 mg. per hundred cubic centimeters.

With rest in bed only the child improved considerably, and after one month was discharged to a convalescent home for the summer. On return, he was placed in a congenial foster home. He attended a class for children with cardiac conditions and was not allowed to participate in any competitive activities.

The child comes regularly to the Growth and Development Clinic. In October 1945 he was adopted by a nice family. He is now in a regular class at school with no limitation of activity. He is 14 years old, a happy normal youngster, apparently in perfect health, and living a normal boy's life. There have been no symptoms of hyperthyroidism for the past five years, and now that the child is in an environment conducive to a nor-

mal happy adolescence, I believe the symptoms have been permanently arrested.

CASE 4—G. N., a boy of 9 years, was admitted March 1, 1938, with a history of tremor, excessive sweating, nervousness and bulging eyes, closely following an attack of pertussis three months previously. Examination on admission showed a basal systolic murmur. Reflexes were hyperactive. There was marked exophthalmos and tremor of the hands. The thyroid gland was enlarged.

The pulse rate was 124; the blood pressure 116 systolic and 60 diastolic; the basal metabolic rate, plus 30 per cent. The cholesterol content was 182 mg. per hundred cubic centimeters. The electrocardiogram showed sinus tachycardia and a tendency to right ventricular preponderance.

Treatment consisted of rest in bed and administration of strong solution of iodine. On this regimen the child began to improve. After one month the family

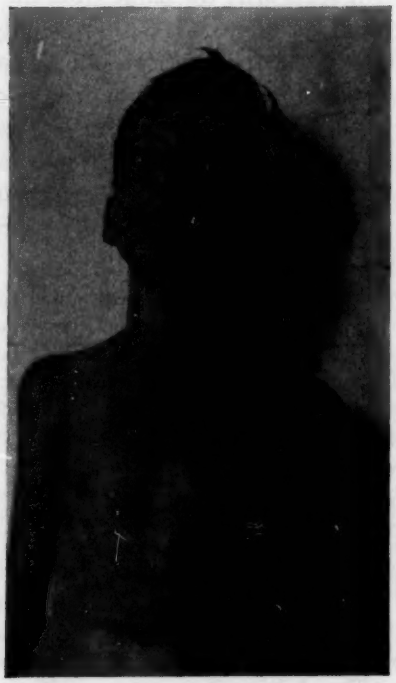

Fig. 4 (case 5).—M. A. as he appeared soon after his first admission to the hospital at the age of 10 years and 4 months.

became impatient and took the child home against advice. Conservative therapy was continued at home. After several months, the child began to get about. He attended a cardiac clinic for the succeeding four years, where persistent tachycardia was noted. On his last visit to the clinic, in April 1942, his blood pressure was 110 systolic and 80 diastolic and the pulse rate 120; the systolic murmur was still present. Soon after this, he began to improve spontaneously. His pulse rate decreased and remained normal.

The boy is now in the third year at high school. He is 18 years old. He has remained symptom free, and, except for some degree of overweight, is well.

CASE 5.—This case (of M. A.) was reported in detail in September 1934 as a case of exophthalmic goiter treated conservatively, with a follow-up of four years (figs. 4 and 5).[9] Briefly, this boy of 10 was admitted to the hospital three times, in acute thyrotoxicosis precipitated by psychic trauma. His last attack was ushered in by convulsive seizures. Treatment was entirely medical. After his third discharge, in September 1930, the boy was observed in the follow-up clinic. He remained free of symptoms of hyperthyroidism for eight years. The seizures never recurred, but the boy had occasional nocturnal attacks resembling petit mal. In December 1938, at the age of 20, the patient died suddenly at home of a cerebral hemorrhage. No postmortem examination was obtained.

Fig. 5 (case 5).—M. A. as he appeared March 22, 1944, at the age of 15 years and 1 month.

The question is raised as to the association between epilepsy and exophthalmic goiter. The only other case in the literature was one reported by Nixon.[5] The patient was a girl of 12½ years who was treated conservatively for exophthalmic goiter. The child did well, and after one year there were no symptoms of hyperthyroidism, except for slight exophthalmos and enlargement of the thyroid gland. This child had "an occasional attack resembling petit mal."

A third case that comes to mind is that of an obese child of 4 years who had attacks of petit mal while taking 2 grains (0.13 Gm.) of thyroid daily. This child never showed symptoms of hyperthyroidism, and the seizures continued long after thyroid therapy had been withdrawn.

9. Topper, A.: J. Mt. Sinai Hosp. 1:107, 1934.

It is of course entirely possible that an unstable nervous system is the common background for both conditions, rather than that exophthalmic goiter bears any causative relationship to the development of the epileptic status. However, I believe one should be wary of using thyroid therapy for any child with an epileptic history, no matter what the indications may be.

CASE 6.—S. N., a 10 year old Puerto Rican girl, was admitted on Dec. 7, 1933. Her past history revealed that in 1931 the child had had scarlet fever, for which she was hospitalized for forty days. Shortly after this, the eyes became prominent, and a staring expression developed (fig. 6). She became nervous and emotionally unstable, and she lost weight in spite of a voracious appetite. Two months before admission, tremor of the hands and fulness of the neck were

Fig. 6 (case 6).—Appearance of S. N. on admission to the hospital.

noted. A moderate degree of dyspnea and palpitation were noted on exertion. There were increased movements of the bowels.

Physical examination on admission revealed marked exophthalmos, tremor of the hands and diffuse enlargement of the neck. All reflexes were hyperactive. The skin was moist. A loud precordial systolic murmur was present. The blood pressure was 132 systolic and 60 diastolic; the pulse rate was 140; the basal metabolic rate was plus 52 per cent. The electrocardiogram was suggestive of poor myocardial function. Roentgenograms of the chest showed moderate enlargement of the heart to the left and right. The cholesterol was 150 mg. per hundred cubic centimeters.

Treatment consisted of rest in bed and administration of strong solution of iodine in addition to a high caloric diet with a high vitamin intake. On this regimen the child's general condition began to improve. Her blood pressure, pulse

rate and basal metabolism gradually became more normal. She began to gain weight.

The child remained in the hospital for three and one-half months. She was then sent to a convalescent home for one month, and then placed in a class for children with cardiac disease in a public school, which she attended regularly for the succeeding three years. During this time she was seen at regular intervals in the follow-up clinic.

The patient is now 24 years old. She has matured satisfactorily. She is entirely symptom free and able to do any type of work Her basal metabolic rate was plus 5 per cent at the last measurement. There is no evidence of exophthalmos.

This was a severe case of exophthalmic goiter with apparent cardiac involvement. The response to medical treatment was excellent, and persists to the present—after a period of fourteen years.

Case 7.[10]—D. D. was first seen on March 1, 1938, at the age of 9½ years, at which time observations at the physical examination were essentially normal. Nine months later, the thyroid gland became somewhat prominent and the pulse rate increased to 100. Syrup of ferrous iodine (0.5 Gm.) was given daily. In September 1939 pertussis developed, from which the child seemed to make an uneventful recovery. Six months later she was again seen at the office. She was nervous. She had lost 7 pounds and looked pale. The thyroid gland was enlarged. The pulse rate was 142; the basal metabolic rate, plus 40 per cent, and the blood pressure, 110 systolic and 50 diastolic.

The child was put to bed and kept there for six weeks, and then gradually allowed a little activity. Two months later the pulse rate was 88, the basal metabolic rate plus 2 per cent. The menarche was established in September 1941, at the age of 13. At this time there were no symptoms or signs of hyperthyroidism. In December 1941 the basal metabolic rate was plus 4 per cent. The child was perfectly well and has remained so to date. She is now 19 years old, in excellent physical condition and leads a normal life.

Case 8.—J. M., a 12 year old Jewish boy, was admitted on Jan. 25, 1940 with a history of nervousness, loss of weight and profuse sweating for several months. All symptoms appeared shortly after the boy's father had been accidentally killed in a machine.

Examination showed moderate exophthalmos, flushed facies, tremor of the hands and an enlarged thyroid gland. The pulse rate was 128; the blood pressure was 130 systolic and 56 diastolic; the basal metabolic rate was plus 38 per cent. The cholesterol content of the blood was 230 mg. per hundred cubic centimeters. There was a flat glucose tolerance curve. The heart showed only a roughened first apical sound. Roentgen examination of the cortices of the radiuses and other long bones revealed some decalcification. The electrocardiogram showed sinus tachycardia and slight slurring of the QRS interval.

The treatment given was rest in bed, administration of phenobarbital and strong iodine solution and a high caloric diet. Vitamin B was given in very large dosage. After two months the boy was discharged. At this time he had gained 3 pounds (1.3 Kg.); his pulse rate was 90; the blood pressure, 112 systolic and 68 diastolic; the basal metabolic rate was plus 11 per cent.

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10. This case was followed by Dr. Murray H. Bass, through whose courtesy it is included in this series.

The boy was observed in the Growth and Development Clinic. At times there were symptoms of hyperthyroidism, which were especially noted at times of stress such as before tests at school. The only treatment during this time was high doses of vitamin B. Competitive activity was not permitted. When the boy was 14 years old symptoms of hyperthyroidism disappeared entirely. The patient is now 20 years old. That he has remained entirely well can be seen from the following excerpt from a letter received from him recently.

I have been in the army for the past year. My health is excellent and I feel fine. I was graduated from the Bronx High School of Science. There I participated in all athletic activities. I played on the basket ball, swimming and soccer teams.

Fig. 7 (case 8).—J. M. in January 1947 after a follow-up of seven and one-half years.

I was nominated for the All City Team. I guess all these activities and the fact that the Army found me physically fit are proof enough of how completely you cured me (fig. 7).

The foregoing 8 patients were treated conservatively. The following 4 were subjected to surgical intervention.

Case 9.—A. B., a Jewish girl 7½ years old, was admitted Feb. 3, 1937 with a history of swelling of the neck, bulging of the eyes and excessive sweating for three weeks—symptoms which appeared immediately after her father had been imprisoned. Examination revealed diffuse enlargement of the neck. A loud bruit was heard over the thyroid gland. The pulse rate was 130; the blood pressure 140 systolic and 65 diastolic; the basal metabolic rate was plus 44 per cent. The cholesterol content of the blood was 220 mg. per hundred cubic centimeters.

After two and a half months of rest in bed and the administration of strong solution of iodine, the child was considerably improved. She was sent to a convalescent home, where administration of iodine was continued. Within one month the child had an acute exacerbation of symptoms and was readmitted to the hospital. At this time the pulse rate was 136; the blood pressure 130 systolic and 48 diastolic, and the basal metabolic rate, plus 40 per cent. Because symptoms had recurred while the child was presumably in a most propitious environment, the question was raised as to whether she would be able to stand the strain of school and play and less favorable home conditions. For this reason, subtotal thyroidectomy was performed. The right lobe and seven-eighths of the isthmus were removed. A second stage operation was considered, but deferred since the child seemed to do well postoperatively.

The child was seen regularly thereafter at the follow-up clinic. The menarche was established at the age of 12 years. Except for slight hypothyroidism (the last basal metabolic rate determined was minus 10 per cent), the patient has grown and developed normally. She was graduated from high school and does secretarial work. She is 19 years old, and was married a few months ago.

Case 10.—C. K., a Jewish girl of 8, was admitted Sept. 12, 1942, with a history of nervousness and serious behavior disturbances for one year. The mother had been operated on for exophthalmic goiter when the child was 4 years old. During the year previous to admission the child had been put to bed for six weeks, had been hospitalized for six weeks and had been in a convalescent home for five weeks. In spite of this, symptoms of hyperthyroidism and the neurotic traits persisted. Prominence of the eyes and fulness of the neck had been noted for several months prior to admission.

On admission, the pulse rate was 120; the blood pressure, 110 systolic and 40 diastolic; the basal metabolic rate, plus 24 per cent; the cholesterol content was 200 mg. per hundred cubic centimters. The child was again treated conservatively for the succeeding three months. On discharge, her pulse rate was 88; the blood pressure was 105 systolic and 55 diastolic, and the basal metabolic rate was plus 4 per cent. The symptoms of hyperthyroidism had improved considerably.

The child was observed irregularly at the follow-up clinic for about one year. There was no loss of weight; blood pressure, basal metabolic rate and pulse rate did not increase. The gland remained unchanged in size, but the exophthalmos became greater. The behavior problems remained unchanged; the child became difficult to manage at home. She was taken to another institution, where a bilateral resection of the thyroid gland was performed in February 1944. The preoperative basal metabolic rate was plus 24 per cent. Immediately after operation the basal metabolic rate dropped to minus 5 per cent. The exophthalmos persisted. The pathologic report was "diffuse toxic goiter with developing Hashimoto struma".

Through the kindness of the surgeon, the record of this child was brought up to date, three years postoperatively. The surgeon writes:

During the past three years, the eye signs have entirely disappeared, the child has become less nervous. The behavior problems are greatly minimized. More recently, she has been well behaved, does very well in school, and conducts herself like any average normal child. At times she has had to have some thyroid support. On March 22, 1947, her basal metabolic rate was minus 12 per cent.

She is now 14 years old. Her pulse rate is 78; her weight 92 pounds [41.7 Kg]. These data would indicate good physical progress.

This case is of special interest because of the evidence of an early Hashimoto strumitis. She is the youngest patient with a case of this kind in our series of some thousands of cases. Incidentally I know of no younger patient mentioned in the literature.

CASE 11.—C. G., a boy of 9, was admitted to the hospital with a history of nervousness for four months. He was suffering from attacks of diarrhea; he sweated profusely and had a marked stare and fulness of the neck. His pulse rate was 130; the blood pressure was 145 systolic and 50 diastolic; the basal metabolic rate was plus 46 per cent. The cholesterol content was 200 mg. per hundred cubic centimeters. The electrocardiogram showed sinus tachycardia and inversion of lead T_2. The sugar tolerance was low.

After three months of conseravtive therapy, the child was discharged, improved. His pulse rate on discharge was 92; blood pressure 120 systolic and 70 diastolic; basal metabolic rate plus 5 per cent. He did not do well at home. All symptoms recurred. The basal metabolic rate rose to plus 25 per cent. He was taken to a surgeon, who performed a subtotal thyroidectomy in January 1935.

A communication received from the surgeon on April 7, 1947, twelve years postoperatively, says:

The boy has remained in excellent health, and his only complaint is that he is unusually tall. In December 1942, he was inducted into the United States Army. His last visit to my office was April 16, 1947. At that time his pulse rate was 84; his weight was 148 pounds [67.1 Kg.]. There were no symptoms or signs of hyperthryroidism. No basal metabolism tests were done postoperatively.

CASE 12.—E. L., a Polish girl of 12, was admitted on Nov. 9, 1936 with a one year history of nervousness and loss of weight, which developed shortly after her parents were legally separated. Tachycardia and exophthalmos were noted for three months preceding admission.

Examination on admission showed all the classic signs of exophthalmic goiter. The pulse rate was 160; the blood pressure, 130 systolic and 60 diastolic; the basal metabolic rate was plus 50 per cent. The cholesterol content was 165 mg. per hundred cubic centimeters. The heart showed marked precordial pulsation, gallop rhythm and a systolic murmur.

The child was put to bed and given strong solution of iodine, phenobarbital and digitalis. Within two weeks the basal metabolic rate decreased to plus 25 per cent, but the tachycardia persisted in spite of all therapeutic measures. Because of the persistent tachycardia for the next three months, a subtotal thyroidectomy was performed in February 1937. The pathologic report was "hyperplastic gland in colloid phase."

Postoperatively, the basal metabolic rate was plus 11 per cent. Within one month it rose further to 40 per cent, and all symptoms of hyperthyroidism recurred. The pulse rate continued to range between 130 and 150. A second stage thyroidectomy was performed in April 1937. Immediately after this all symptoms abated. The basal metabolic rate fell to minus 3 per cent. The exophthalmos persisted and the tachycardia remained unchanged for two months after operation. In September 1937, the child began to menstruate. Soon after the pulse rate become normal. The exophthalmos did not disappear entirely until December 1940.

Significant Data for 12 Children With Exophthalmic Goiter

	8 Treated Medically								4 Treated Surgically			
Case No. and Sex	1 A.K. ♀	2 D.S. ♀	3 I.F. ♂	4 G.N. ♂	5 M.A. ♂	6 S.N. ♀	7 D.D. ♀	8 J.M. ♂	9 A.B. ♀	10 C.K. ♀	11 C.G. ♂	12 E.L. ♀
Age in years	3½	7	8½	9	10	10	11½	12	7½	8	9	12
Etiologic factor	Ketosis	Infection	Psychic trauma	Infection	Psychic trauma	Infection	Pertussis	Psychic trauma	Psychic trauma	Familial	?	Psychic trauma
Duration of symptoms	1 mo.	1 yr.	2 yr.	3 mo.	1 yr.	2 yr.	2 yr.	8 mo.	3 wk.	1 yr.	4 mo.	1 yr.
Loss of weight	—	+	+	—	+	+	+	+	—	+	—	+
Nervousness	+	+	+	+	+	+	+	+	+	+	+	+
Tremor	+	+	+	+	+	+	—	+	+	+	+	+
Exophthalmos	+	+	+	+	+	+	—	+	+	+	+	+
Enlargement of gland	+	+	+	+	+	+	+	+	+	+	+	+
Pulse rate	150	120	120	124	122	140	142	128	130	120	130	160
Blood pressure	—	124/70	128/70	116/60	140/55	132/60	110/50	130/56	140/65	110/40	145/50	130/60
Basal metabolic rate	50%	30	25	30	49	52	40	38	44	24	46	50
Cholesterol mg. per 100 cc.	—	—	190	182	188	150	200	230	220	200	200	165
Lymphocytes, per cent	—	58	34	40	54	44	47	50	58	55	48	54
Duration of follow-up	25 yr.	3½ yr.	5	9	10	14	7½	7½	11½	5	12	10
Present status	Normal	Lost	Normal	Normal	Deceased	Normal	Normal	Normal	Occ. hypothyr. well	Occ. hypothyr. well	? hypothyr. well	Occ. hypothyr. well

The patient has been seen regularly in the follow-up clinic. She is now 23 years old. Except for occasional hypothyroidism, she is entirely well and is unlimited in her activities.

The table summarizes the significant data in all 12 cases. From this table, certain characteristics of exophthlamic goiter are brought out. It will be seen that the classic signs and symptoms of this disease, namely nervousness, tremor, tachycardia, exophthalmos and enlargement of the thyroid gland, were present in 11 of the 12 children. Patient 7 never showed definite exophthalmos or tremor of the hands, but all the other symptoms mentioned were well marked.

Etiologic factors include acute infection in 4 cases, psychic trauma in 5, ketosis in 1 case and in 1 familial endocrine history. In 1 case there was no discoverable precipitating cause.

The basal metabolic rate on admission was high in all cases, the range being from plus 24 per cent to plus 52 per cent.

There was a history of loss of weight in 9 cases. Of course an accurate history of the exact sequence and duration of symptoms is fairly difficult to obtain, since the onset of the disease may be insidious. However, in general, the loss of weight seemed to parallel the duration of symptoms rather than the severity of the process.

The cholesterol content of the blood ranged from 150 mg. to 230 mg. per hundred cubic centimeters and showed no consistent relationship with the severity of the disease.

Although lymphocytosis is often found in exophthalmic goiter, there was no consistent increase of lymphocytes in this series.

The blood pressure invariably showed an increased systolic and a lowered diastolic reading, with resulting increase in the pulse pressure. This tended to become normal in all cases after the symptoms had been arrested.

Of the 8 patients treated conservatively, I died from an apparently unrelated cause after being well for ten years (case 5); 1 child was lost track of after she had been symptom free for three and one half years (case 2); the remaining 6 patients are well and living normal lives today, after a follow-up period varying from five to twenty-five years.

Of the 4 patients treated surgically, there is a definite history of postoperative hypothyroidism in 3 of them. No follow-up basal metabolism tests were done on the fourth. These patients are all doing well.

COMMENT

In retrospect, there is no way of determining whether the 4 children who were subjected to surgery might have been spared operation. In case 9, there was a recurrence of symptoms while the child was presumably in the most favorable environment. In this case the entire his-

tory was very short, thyroidectomy having been performed within four months after the onset of symptoms. Perhaps a longer period of conservative management should have been allowed.

Case 10 was unusual, in that the pathologist reported a "Hashimoto strumitis." This type of chronic lymphoid thyroiditis is extremely rare in childhood. It usually causes pressure symptoms. In this case there were no symptoms of this type; but the mother had a difficult time in managing the child, who had serious neurotic traits. She took her to another institution, where operation was performed. Means[11] believes that in this type of goiter roentgen treatment should have a short trial. If the goiter rapidly disappears, one is justified in pursuing "a course of watchful waiting."

In case 11, although all symptoms appeared to be mild, the parents became impatient when the disease did not abate after one year, and took the child to another institution, where thyroidectomy was performed.

In case 12, thyroidectomy was performed because of the persistent tachycardia. The girl was 12 years old—in the prepuberty period. At this time, there is a change in the endocrine balance. The ovarian gland tends to become increasingly active, while thyroid activity becomes subdued. Had treatment been conservative, there might have been a spontaneous arrest of symptoms. As to the effect of the persistent tachycardia, perhaps there was no need to be unduly worried, since the myocardial reserve is evidently equal to prolonged strain in childhood, and coronary disease does not occur. Case 1 was a notable example of how much the heart can stand without permanent damage. Here, tachycardia had persisted for many years, with actual myocardial involvement; yet today, at the age of 29½ years, the patient is entirely well and the heart perfectly normal.

In 3 of the 4 children subjected to surgery, transient hypothyroidism developed. Tests were not performed on the fourth. All 4, however, are well today, and living apparently normal lives.

Of the 8 children treated conservatively, 1 died at the age of 20, apparently from an unrelated condition. He had been symptom free for ten years preceding death (case 5). One child was lost track of after being well for three and one half years (case 2). The other 6 patients, after periods of from five to twenty-five years, are well and leading normal lives.

In spite of the small number of cases, these satisfactory results give support to the advocates of the conservative management of exophthalmic goiter in childhood.

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11. Means, J. H.: Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 503.

The thyroid gland plays such an important role in growth and development that it would seem advisable to avoid surgical removal whenever possible. The question of the amount of thyroid tissue to be removed is always problematic, since future demands on the gland are unpredictable. As a matter of fact, thyroidectomy, even when most skilfully performed, and with the best of results, is not the answer to the problem of a disease in which the cause is still uncertain. As Means[12] has aptly said:

> In the final analysis, surgical operations should be looked upon as ideal treatment only for purely mechanical conditions. It is impossible to conceive of a better treatment for, let us say hernia, than surgical repair. It is quite possible, however, to imagine at least, a form of treatment for toxic goitre which will in some non-surgical fashion remove or render ineffective the primary cause of the disease.

This statement seems prophetic in the light of recnt investigations, since such "a form of treatment" is being tried today with the use of thiouracil and its related compounds.[13] These drugs block the synthesis of the thyroid hormone. They have toxic effects, however, especially on the hemopoietic system. Propylthiouracil, which seems to be superior to thiouracil and less toxic, is being investigated in many clinics.[14] To date, there have been no published reports of its effectiveness in children. Wagner[15] is treating 2 children with this drug. The children are ambulatory, and remain symptom free while taking the drug; but as soon as the drug is withdrawn symptoms recur.

Results reported with radioactive iodine, which can be given orally, also seem to be promising.[16] It would be premature, however, to draw any definite conclusions at this time.

Although both propylthiouracil and radioactive iodine cause temporary remissions, it is impossible to state at this time whether they effect permanent cures. However, when hyperthyroidism occurs in

12. Means,[11] p. 577.

13. Barr, D. P., and Shorr, E. Ann. Int. Med. **23**:734, 1935. Himsworth, H. P.: Proc. Roy. Soc. Med. **37**:693, 1944. Rose, E., and McConnel, J.: Am. J. M. Sc. **208**:561, 1944. Williams, R. H., and Clute, H. M.: Thiouracil in Treatment of Thyrotoxicosis, J. A. M. A. **128**:65 (May) 1945. McGavack, T. H., and others: J. Clin. Endocrinol. **5**:259, 1945. Palmer, M. V.: Ann. Int. Med. **22**:335, 1945. Means, J. H.: ibid. **25**:403, 1946. Williams, R. H.: J. Clin. Endocrinol. **6**:1, 1946. Aranow, H., Jr., and others: Ann. Surg. **124**:167, 1946. Beierwaltes, W. H., and Sturgis, C. C.: Remissions in Thyrotoxicosis After Discontinuing Thiouracil, J. A. M. A. **131**:735 (June 29) 1946.

14. Astwood, E. B., and Vanderlaan, N. P.: J. Endocrinol. **5**:424, 1945. Astwood, E. B.: Bull. New England M. Center **7**:202, 1945. McCullagh, E. P.; Ryan, E. J., and Schneider, R.: Cleveland Clin. Quart. **13**:232, 1946.

15. Wagner, R.: Personal communication to the author.

16. Thompson, W. O., and Spies, T. D.: The 1946 Year Book of Endocrinology, Metabolism and Nutrition, Chicago, The Year Book Publishers, Inc., 1946, editor's note, p. 28. Means, J. H.: Ann Int. Med. **25**:403, 1946.

children, it is important to allay the symptoms even temporarily, until puberty, at which time there is a revolution in the endocrine orchestra and the thyroid gland plays a less prominent role. This makes it possible to obviate the removal of a gland which is so important to the growing and developing organism.

SUMMARY AND CONCLUSIONS

A follow-up study was made on 12 children seen during the past twenty-five years suffering from exophthalmic goiter. Eight of these children were treated conservatively; 4 were subjected to thyroidectomy.

These children have now been observed for periods varying from three and one half years to twenty-five years.

Of the 8 children treated medically, 1 died of an apparently unrelated condition ten years after all symptoms of exophthalmic goiter had been arrested. One child was lost track of after being well for three and one half years. The other 6 are still under observation, after a follow-up period of from five to twenty-five years. They are all entirely well and leading normal lives.

Of the 4 children treated surgically, 3 have had occasional hypothyroidism, which responded readily to treatment. The fourth did not have any basal metabolism tests postoperatively. All 4 are doing well, after a period of five to twelve years. However, one is tempted to speculate as to whether operation might have been avoided in these children.

Since the advent of iodine therapy,[17] the prognosis of thyroidectomy has been markedly improved, and there seems to be little question as to the advisability of this procedure in adults. In childhood, however, one hesitates to remove a gland that is so important for growth and development. During puberty, there is a change in the endocrine activity, the gonads assuming greater importance and thyroid activity becoming more subdued, as the need for growth becomes subordinate to the need for maturation. Anything that will cause even temporary remission of the symptoms of hyperthyroidism until puberty is established would be advantageous.

Recent investigations seem to indicate that propylthiouracil produces at least temporary remissions. Results reported with radioactive iodine are also promising. There are still not enough data to warrant drawing any definite conclusions concerning permanent cures as a result of these substances.

At any rate, it is incumbent on the pediatrician to continue the search for satisfactory medical treatment of exophthalmic goiter when it occurs before puberty.

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17. Plummer, H. S., and Boothby, W. M.: Illinois M. J. **46**:401, 1924. Plummer, H. S.: J. Iowa M. Soc. **14**:66, 1924.

PERFORATED ADHESIVE TAPE FOR UMBILICAL HERNIAS

ROBERT COHEN, M.D.
STUDIO CITY, CALIF.

THE PURPOSE of this report is to introduce a multiple perforated adhesive tape for use in strapping acquired umbilical hernias in infants, and to show that it is more beneficial than the plain adhesive tape that is in common use at the present time.

The accepted procedure in treating acquired umbilical hernias mentioned in standard pediatric and surgical textbooks is that of first digitally reducing the hernial protrusion and then securing it by the use of adhesive plaster over the area. Technical variations are usually mentioned, but all in all the discrepancies in the advantages of one over the other is so small that it will not be mentioned.

On removing the standard brands of tape after a period of seven to ten days, various dermatologic manifestations will be found, depending on such factors as domestic care, allergic conditions, sensitive skin and climatic influence.

The more common conditions seen are erythematous zones, excoriations, capillary bleeding, pinpoint vesiculations and pustulations, impetigo, wrinkling of the skin and sudamina miliaria. Some of these conditions cause a delay of one to three days before retaping can be done in order that healing of the lesions may take place. The days lost added up over a period of six months constitute a long enough interval to delay the closure of the hernia even to the point of weakening the hernia because of lack of support.

According to Ylppo[1] 84 per cent of the premature infants have either umbilical or inguinal hernias, and Homans[2] states that in the infancy period the umbilical hernias are common. The latter fact is self evident to those in pediatric practice.

It is good standard pediatric practice to assist by the use of prophylactic taping of the umbilical hernia until spontaneous closure ensues or

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Mr. E. E. Dickson of Johnson and Johnson and Dr. J. Henderson, Director of their Clinical Research Department, supplied this tape marked #3358, experimental type.

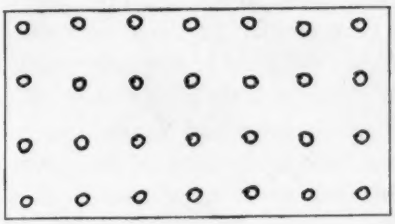
1. Ylppo, A.: Ztschr. f. Kinderh. **24**:1, 1919.

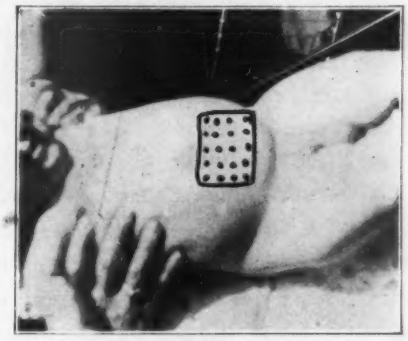
2. Homans, J.: A Textbook of Surgery, ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1936.

until the infant becomes a candidate for surgical repair. The good it does warrants every possible assistance to this procedure.

Adhesive tape with multiple perforations was tried on 50 infants having acquired umbilical hernias and compared with 50 controls on whom the standard nonperforated adhesive brands on the market today was used. The tape used was 2 inches (5.08 cm.) wide, multiple perforated, ⅛ inch (0.32 cm.) in diameter and spaced at ½ inch (1.27 cm.) intervals. There were four perforations to the width.

These facts were noted in the comparison with the plain tape: 1. It allowed more surface ventilation by exposing more normal skin for aeration. 2. A photographic exposure meter showed that twenty times more light passed through the perforated type. 3. Less adhesive plaster was used. 4. A 2 by 6 inch (5.08 by 15.2 cm.) perforated tape weighed





Perforated tape: its application.

1.8 grains (0.11 Gm.) less than a strip of the same dimensions unperforated.

On removal of the perforated tape after a usage of seven to ten days it was noted that: 1. Rows of dotted normal skin ⅛ inch in diameter corresponding to the perforations of the tape were present. They seemed to assist in fixing the tape better by acting as small islands for anchoring. 2. There was 50 per cent less irritation of the skin in respect to erythema and excoriations. 3. Bleeding did not occur. 4. Pustulations or vesiculations were not seen in this series. 5. The infants that were allergic to the substance of the tape showed less areas of irritation. 6. The controls did not have as good results as those on whom the perforated tape was used. 7. The area could be immediately cleaned and retaped without loss of time or setbacks.

CONCLUSION

Because of at least 50 per cent improvement in the use of the multiple perforated adhesive tape over the plain tape as shown by less dermatologic lesions, this tape is recommended in the prophylactic taping of acquired umbilical hernia in infancy.

RHEUMATIC INFECTION IN CHILDHOOD: FIFTEEN TO TWENTY YEAR FOLLOW-UP

Caution Against Early Ambulant Therapy

RACHEL ASH, M.D.
PHILADELPHIA

IN A PREVIOUS paper[1] an analysis was presented of the outcome of rheumatic infection ten years after onset in a group of patients whose initial illness had occurred during the period 1923 to 1937, inclusive. The original group comprised 588 children, of whom 537 (91.3 per cent) had been located at the end of the ten year period. At the termination of the initial attack, 60 per cent had shown evidence of the presence of rheumatic heart disease. Of these 318 children with clinical evidence of heart disease at onset, signs of cardiac involvement had disappeared in 9 per cent. Forty-two per cent of those with early signs of rheumatic heart disease had died of rheumatic infection or bacterial endocarditis.

Of 219 patients without clinical evidence of heart disease at the termination of their first attack, 77 per cent still did not show evidence of heart disease ten years after onset. Only 5 per cent of this group with potential heart disease at onset had died subsequently of rheumatic infection or bacterial endocarditis.

Ten years after onset, 60 per cent of these rheumatic patients were leading a normal existence with little or no limitation of activity. Eleven per cent were suffering from symptoms due to cardiac failure or to active rheumatic infection. Death due to rheumatic infection had occurred in 24 per cent. In addition, 12 patients had died of bacterial endocarditis and 8 of unrelated causes.

Many patients were followed for a period of time greater than ten years. In the present paper the further outcome of the infection will be presented among those who were followed for fifteen and for twenty years.

In the fifteen year follow-up series (table 1) the original group comprised 391 children, of whom 365 were followed for one year, 360 for

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From the Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania Medical School.

All percentages throughout this paper are based on the number of patients traced at each time period.

1. Ash, R.: The First Ten Years of Rheumatic Infection in Childhood, Am. Heart J. **36**:89,1948.

five years, 349 for ten years and 331 for the full fifteen year period. At the end of ten years, 212 (60.7 per cent) were able to lead a normal life with little or no restriction of activity; 32 (9.1 per cent) were limited as to activity either because of some degree of heart failure or as a result of active rheumatic infection, and 29.2 per cent were dead of rheumatic

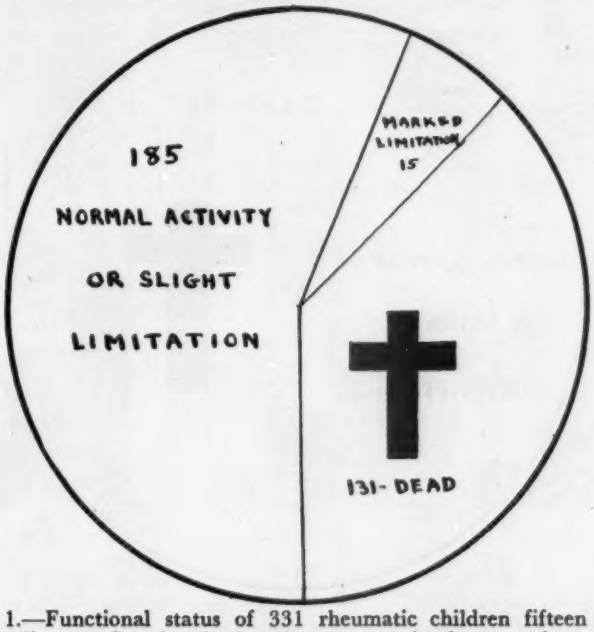

Chart 1.—Functional status of 331 rheumatic children fifteen years after onset of the disease. One hundred and seventeen deaths were due to rheumatic infection with or without an associated acute infection, 8 to bacterial endocarditis and 6 to unrelated causes.

TABLE 1.—*Outcome of Rheumatic Infection in a Group of Children Observed for Fifteen Years Following Onset*

No. Traced	Per Cent of Total Group	Rheumatic Heart Disease		Deaths				Duration, Years
				Rheumatism		Subacute Endocarditis No.	Other Causes No.	
		No.	Per Cent	No.	Per Cent			
365	93.4	239	65.5	33	9.0	0	0	1
360	92.0	242	67.2	71	19.7	3	2	5
349	89.3	241	69.1	96	27.5	6	3	10
331	84.6	232	70.1	117	35.3	8	6	15

infection or bacterial endocarditis. At the end of fifteen years, 185 (55.9 per cent) were leading a normal existence, 15 (4.5 per cent) were limited in activity and 125 (37.4 per cent) were dead of rheumatic infection or bacterial endocarditis (chart 1).

In the twenty year follow-up series (table 2) the original group comprised 184 children, of whom 176 were followed for one year, 175 for five years, 173 for ten years, 164 for fifteen years and 150 for the full twenty year period. At the end of ten years, 98 (56.6 per cent) were able

to lead a normal life, 8 (4.6 per cent) were definitely limited in activity as a result of congestive heart failure and 64 (37 per cent) were dead of heart disease. Five years later the number of those dead had risen to 74 (45.4 per cent), and the number able to lead a normal life was 81 (49.4 per cent), with 4 persons (2.4 per cent) markedly limited in

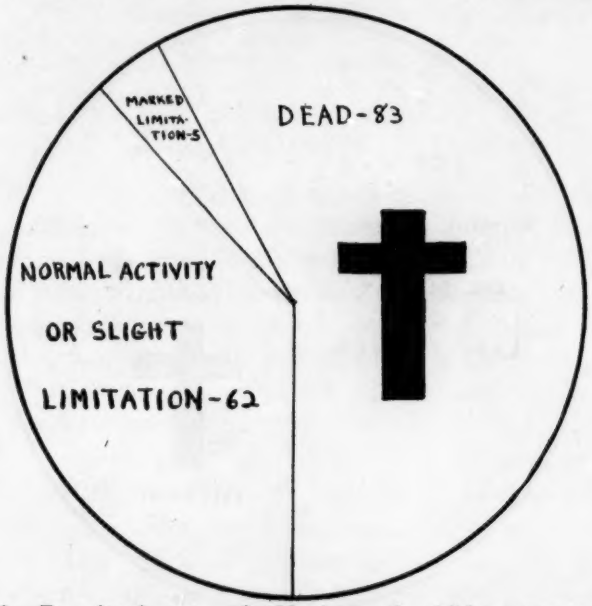

Chart 2.—Functional status of 150 rheumatic children twenty years after onset of the disease. Seventy-three deaths were due to rheumatic infection with or without an associated acute infection, 6 to bacterial endocarditis and 4 to unrelated causes.

TABLE 2.—*Outcome of Rheumatic Infection in a Group of Children Observed for Twenty Years Following Onset*

No. Traced	Per Cent of Total Group	Rheumatic Heart Disease		Deaths				Duration, Years
				Rheumatism		Subacute Endocarditis No.	Other Causes No.	
		No.	Per Cent	No.	Per Cent			
176	95.6	118	67.1	22	12.5	0	0	1
175	95.1	125	71.4	43	24.6	2	2	5
173	94.0	118	68.2	60	34.7	4	3	10
163	83.1	116	71.1	68	41.7	6	4	15
150	81.5	114	76.0	73	48.7	6	4	20

their ability to undertake physical activity. At the end of twenty years only 81.5 per cent of the group had been located. Of these 150, 79 (52.6 per cent) were dead, 62 (41.3 per cent) were leading a normal existence and 5 (3.3 per cent) were suffering from congestive heart failure (chart 2).

Whether one looks on these figures with optimism or with pessimism depends perhaps on one's temperament. The optimist would stress the fact

that approximately 60 per cent of this group of rheumatic children were leading a normal life at the end of ten years and 56 per cent at the end of fifteen years. The pessimist would point to the fact that approximately one quarter of the group were dead at the end of ten years, well over one third at the end of fifteen years and one half at the end of twenty years.

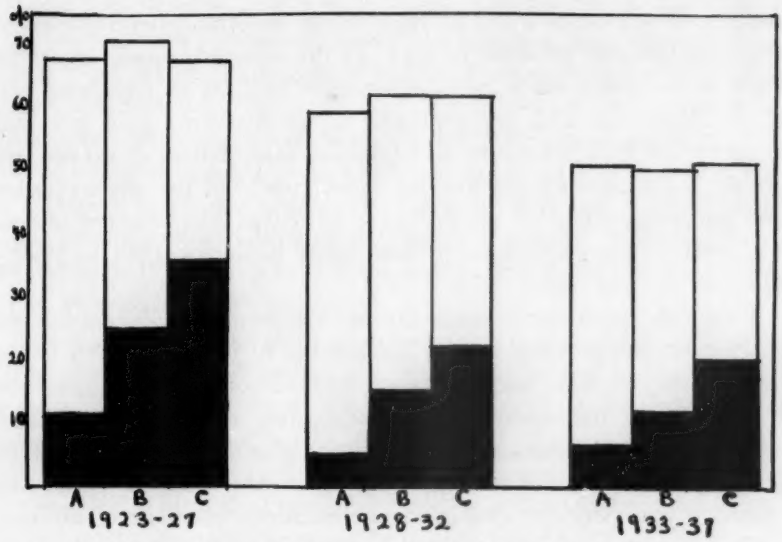

Chart 3.—Trend toward lessening of severity of rheumatic infection over a fifteen year period. Column *A* indicates the incidence of cardiac involvement at the end of one year with onset of infection during the years noted; column *B*, the incidence of cardiac involvement at the end of five years; column *C*, the incidence of cardiac involvement at the end of ten years. The shaded areas indicate the percentage of deaths due to rheumatic infection or bacterial endocarditis.

TABLE 3.—*Decline in Incidence of Carditis and of Deaths Among Rheumatic Children Taken Ill During Successive Five Year Periods*

	Incidence Onset 1923 to 1927	Incidence Onset 1928 to 1932	Incidence Onset 1933 to 1937
Rheumatic heart disease during initial illness	68.4	59.4	50.9
Rheumatic heart disease at 5 years	71.5	62.3	50.5
Rheumatic heart disease at 10 years	68.2	62.3	51.0
Deaths during initial illness	11.9	5.6	6.3
Deaths at 5 years	26.8	15.0	12.6
Deaths at 10 years	36.4	21.7	20.5

There is a more favorable aspect to the picture, however. The incidence of carditis and of deaths within the first ten years was greater among those taken ill during the period 1923 to 1927 than during the years 1928 to 1932 and least of all among those taken ill during the years 1933 to 1937, inclusive (table 3, chart 3).

The lowering of mortality and of the incidence of obvious cardiac involvement within three successive five year periods starting with 1922 had been noted in a previous follow-up study of this group.[2] It was pointed out that part, although not all, of this improvement might be due to a spontaneous change in the character of the disease. Hedley in 1939 called attention to the decrease in mortality from heart disease since 1922 among persons between 5 and 24 years of age, a period when rheumatism is the most frequent etiologic factor.[3] In the Middle Atlantic States the decline in the mean death rate during 1930 to 1936 as compared with 1922 to 1929 was 27.2 per cent and in Pennsylvania 24.5 per cent. Among the patients treated at the Children's Hospital the death rate due to heart disease during the first ten years following the onset of rheumatic infection within the years 1933 to 1937 was 20.5 per cent as compared with 36.4 per cent among those taken ill during 1923 to 1927, a decline of 43.4 per cent.

A shift in racial composition during the period of observation was mentioned in the previous report, the number of Negro children having shown a slow increase. Such a change, however, should have influenced the situation for the worse since the death rate among Negro children has been higher than among white children. The distribution of children according to type of onset has shown no significant variation within each of the five year periods. The incidence of cardiac damage of sufficient severity to present obvious clinical signs has shown a decline chiefly among those who presented arthritis as an initial manifestation. The diagnosis of rheumatic infection is admittedly controversial in the group of children with arthritis but without clinical signs of carditis. The criteria of diagnosis used throughout this period have however been unchanged. Since the group described in the present paper includes all patients with rheumatic infection whether treated under the supervision of the outpatient department or whether admitted to the wards, the results cannot be due to any change in policy regarding admissions.

The decline in the incidence of carditis cannot be ascribed to any variation in the method of using salicylates. Throughout this period it has been the custom to administer large doses of salicyalates at the beginning of the disease if symptoms were sufficiently severe but not to continue the use of salicylates in the absence of fever and pain in the joints. In repeated isolated instances the development of carditis and of acute exacerbations of rheumatic infection has been noted while large doses of salicylates were being administered.

2. Ash, R.: Rheumatic Infection in Childhood; Influence of Type of Onset and Calendar Year of Onset, Am. Heart J. **22**:439, 1941.

3. Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality from Heart Disease Among Persons Five to Twenty-Four Years of Age in the United States During Recent Years (1922-1936): Preliminary Report, **54**:2271, 1939.

About 1928, under the guidance of Dr. J. C. Gittings and the late Dr. Horace Jenks, the use of adequate doses of digitalis in the treatment of heart failure associated with acute rheumatic carditis was begun. Probably a few children in this series were pulled over a critical period by the use of this drug and thus enabled to live long enough to marshall their own defenses against the disease. At the Children's Hospital digitalis has been found most useful in the treatment of children in whom dyspnia is the predominant manifestation of heart failure and of much less value in those with predominant signs of failure of the right side of the heart—marked enlargement of the liver and edema. About 1935, routine tonsillectomies were discontinued.[4] Since then, if there has been need for the removal of tonsils the operation has been performed only at a time when the infection was considered to be inactive. The use of diuretics has played little if any part in whatever improvement has occurred, since it was not until 1941 that xanthine derivatives and mercurial diuretics began to be used with any regularity.

The major change in treatment during this period would seem to pertain to the duration of stay in the hospital or of rest in bed at home. Whereas in the early part of this period the majority of children were returned home shortly after the disappearance of acute symptoms, these children are now left in the hospital for an average period of three months, after which they are discharged to a convalescent home or if sent home remain under the supervision of the Visiting Nurse Society and the Rheumatism Clinic until all signs of active infection have disappeared. Rest in bed in the presence of active rheumatic infection is recommended regardless of the presence or absence of clinically recognizable heart disease.

Whether the lessening of severity of the disease during this period is partly due to the favorable influence of prolonged rest in bed at the onset of infection or entirely due to a spontaneous change in the character of the disease can be a subject for speculation only, but it would seem wise for pediatricians to give prolonged rest in bed the benefit of the doubt and not to be tempted to try the recently instituted Army Air Force program of early ambulation.[5] Adults are more stable in their reactions to rheumatic infection than children. The over-all incidence of carditis among 10,000 cases of rheumatic fever in the Army was 10 per cent.[6] (0.13 per cent) with rheumatic fever. A relatively benign illness, such as

4. Ash, R.: Influence of Tonsillectomy on Rheumatic Infection, Am. J. Dis. Child. **55**:63 (Jan.) 1938.

5. Robertson, H. F.; Schmidt, R. E., and Feiring, W.: The Therapeutic Value of Early Physical Activity in Rheumatic Fever: Preliminary Report, Am. J. M. Sc. **211**:67, 1946.

6. Stroud, W. D.: Personal communication to the author.

Only thirteen deaths occurred in over 10,000 patients of military age[7]

7. Griffith, G. C.: Rheumatic Fever: Its Recognition and Treatment, J. A. M. A. **133**:974 (April) 1947.

these figures reflect, bears little comparison to the ominous form of the disease which occurs in childhood. In the present group, for instance, some 60 per cent of the children presented signs of heart disease at onset and almost 10 per cent had died within the first year.

During the earliest period covered by this study (1923 to 1927) early ambulation was, in fact, the prevalent method of treatment. Criteria for the indication of inactivity of the infection were not well established. Many children were discharged to their homes or sent to the Philadelphia Heart Hospital in an early phase of the disease. At the Heart Hospital full lavoratory privileges were granted. There were repeated returns of these children to Children's Hospital in a worse stage of the disease. The death rate during this period was excessively high.

Further evidence of the value of rest has been provided by Taussig and Goldenberg[8] in a study of changes in the size of the heart as ascertained by the means of teleoroentgenograms in a large series of cases of rheumatic heart disease. Children without demonstrable increase in the size of the heart and those in whom cardiac enlargement had failed to progress were found to be those who had been kept at complete rest in bed for long periods. Only 50 per cent of the group in which there was progressive cardiac enlargement had been kept in bed and these for only short periods during the acute phase of their illness. The remainder did not have rest in bed until their terminal illness.

SUMMARY

The results of a follow-up study of 331 rheumatic children fifteen years following the onset of their infection and of 150 children twenty years following the onset of their infection are presented.

The incidence of carditis and of deaths during the first ten years following onset was greater among children taken ill during the period 1923 to 1927 than during the years 1928 to 1932 and least of all among those taken ill during the years 1933 to 1937.

Although a spontaneous change in the character of the disease has probably occurred during this period, the favorable influence of prolonged rest in bed at onset would seem also to have played a part. It is urged that pediatricians be not tempted to institute early ambulant treatment in the care of the rheumatic child.

NOTE.—Since this paper was written an article by Dr. L. M. Taran[9] has come to my attention. In this article he furnishes additional evidence based on his experience at St. Francis Sanatorium for Cardiac Children establishing the value of prolonged rest in bed in the treatment of children with rheumatic infection.

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8. Taussig, H. B., and Goldenberg, M.: Roentgenologic Studies of the Size of the Heart in Childhood: I. Three Different Types of Teleoroentgenographic Changes Which Occur in Acute Rheumatic Fever, Am. Heart J. **21**:2, 1941.

9. Taran, L. M.: The Treatment of Acute Rheumatic Fever and Acute Rheumatic Heart Disease in Children, M. Clin. North America **31**:557, 1947.

GRAPHIC PORTRAYAL OF INFANTS' GROWTH WITH CONSIDERATION OF HEAD SIZE

JULIAN D. BOYD, M.D.
IOWA CITY

PHYSICAL MEASUREMENTS of the infant or child provide a valuable index of individual progress. Deviant measurements often serve as important evidence of disease. Unless accurate measurements comprise a part of every physical examination, the physician deprives himself of a valuable clinical tool.

The measurements themselves, however, reveal but little. To gain significance, they must be compared with suitable standards, and the normal limits of variability must be known. The measurements obtained from a normal population of infants and children should be used as a basis for reference. In the choice of the reference group, it is better to use subjects who have been reared under favorable environmental conditions than a more random sample. With improved conditions of living, children tend to be larger for their age and to grow at a more rapid rate than those whose pattern of living has been commonplace or inferior.[1] By using the more select standards, the examiner is better able to determine the degree to which his subject is approximating his presumed capacities and to detect unsuspected agencies which may be affecting growth adversely.

In the pediatric clinic of Children's Hospital the measurement matterials reported by Meredith and Boynton have proved satisfactory for clinical appraisal.[2] Meredith's values were obtained from subjects living under acceptably good environmental conditions. His averages and range

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From the Department of Pediatrics, State University of Iowa College of Medicine.

1. Sanders, B. S.: Environment and Growth, Baltimore, Warwick & York, Inc., 1934.

2. Meredith, H. V.: The Rhythm of Physical Growth: A Study of Eighteen Anthropometric Measurements of Iowa City White Males Ranging in Age Between Birth and Eighteen Years, University of Iowa Studies, Iowa City, University of Iowa Press, 1935, vol. 11, no. 3. Boynton, B.: The Physical Growth of Girls: A Study of the Rhythm of Physical Growth from Anthropometric Measurements on Girls Between Birth and Eighteen Years, ibid., 1936, vol. 12, no. 4; unpublished revised distributions of height and weight measurements of Iowa City children.

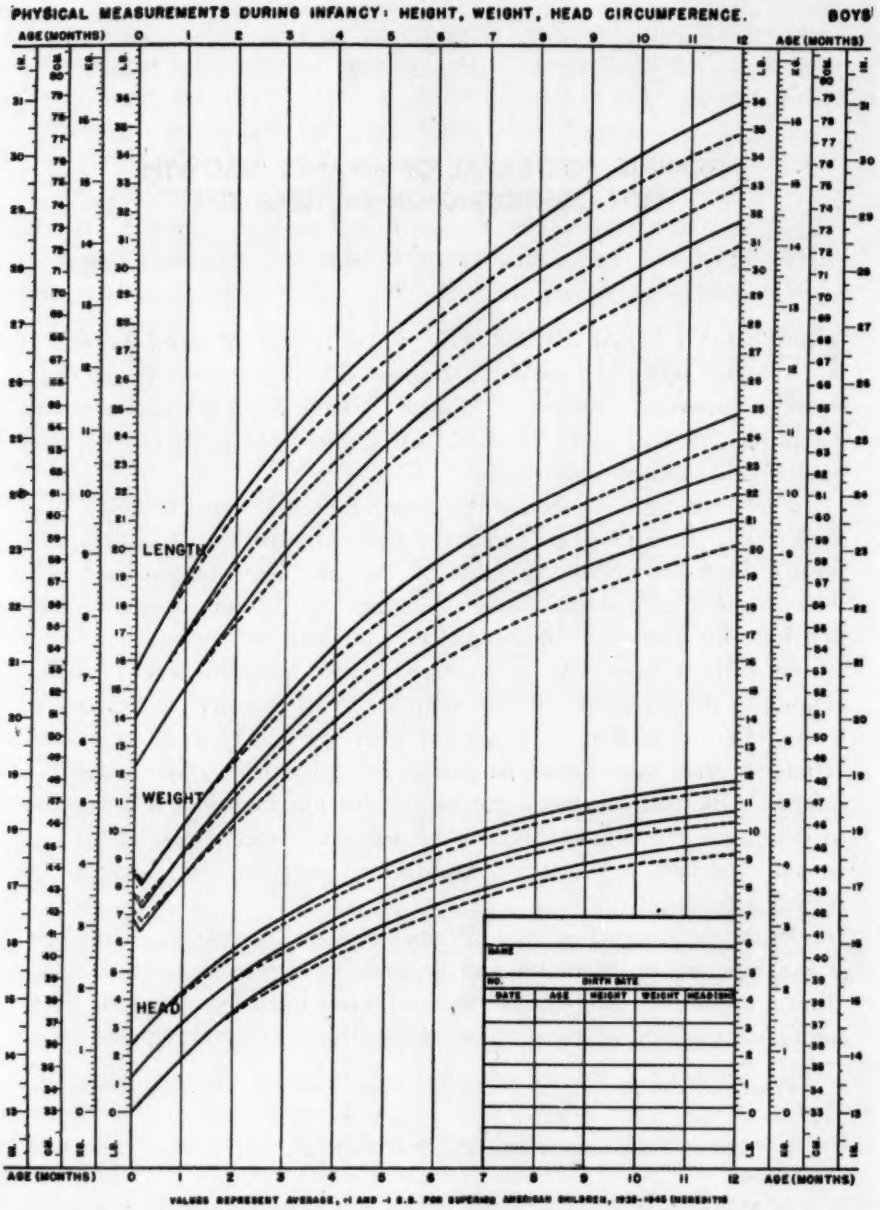

Chart 1.—The solid lines represent curves for growth for the standard population of male infants from birth through the twelfth month. For each dimension, the middle curve indicates the average values for age; the upper and lower curves bound the range of values observed for approximately two thirds of the standard population (Meredith).

The broken lines do not appear on the standard record form. They are added to indicate the slope of the curves for corresponding measurements of female infants (fig. 2). To facilitate comparison of the slopes, measurements at birth of girls have been placed in superposition with those for boys. The actual values lie slightly below the indicated positions throughout infancy. However, it will be evident that when infants of similar initial length are compared, little difference due to sex need be expected between contrasted measurements.

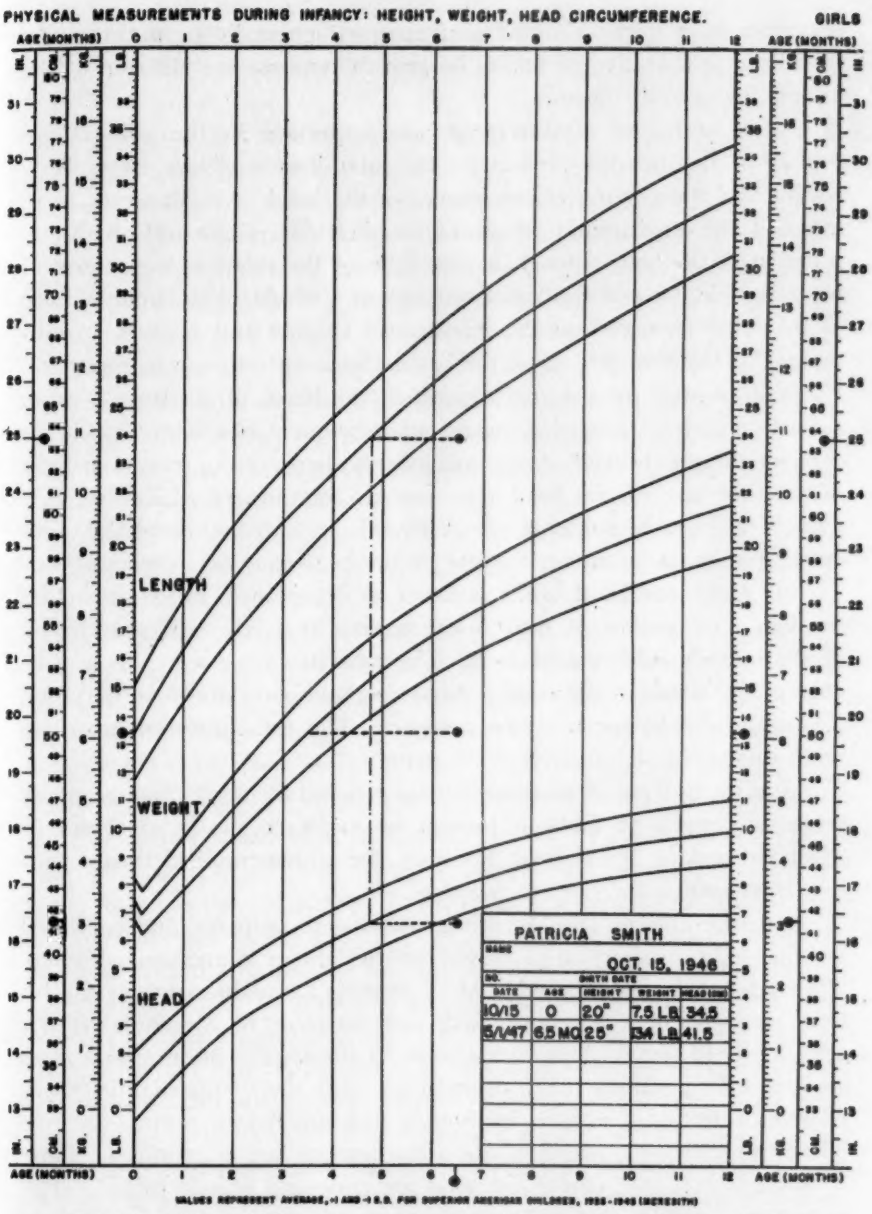

Chart 2.—The solid lines represent curves for growth for the standard population of female infants from birth through the twelfth month (see legend for figure 1).

For illustrative purposes the measurements of a 6½ month old girl are plotted. All measurements fall outside the usual zone for her age. By projecting each measurement horizontally until it intersects the average curve for age, as illustrated by the dotted lines, it will be noted that the weight agrees with that of the average 3½ month old infant, whereas both body length and head circumference correspond with those for the average infant of 4.7 months. Thus, this infant is underweight for height, underheight for age, with a head size which corresponds with its body length but not with its age. It would be reasonable to predicate that the slow general growth has been conditioned by undernutrition or by disease which has interfered with food intake or utilization, and that the head size probably is within normal limits for this particular infant.

of values have been validated and accepted generally by anthropometrists as representative of favorable growth response for children of the United States and Canada.

Three principal measurements are important in the clinical appraisal of the infant's physique: the total length of the body, body weight and the greatest circumference of the head. Length serves as an index of the longitudinal growth of the skeleton; weight reflects the total mass of the body, though it tells little of the relative proportions of bone, muscle, fat and fluid in the tissues as a whole. The circumference of the head is related to the intracranial volume and permits an estimate of the rate of growth of the brain. Such an estimate is important. Normally during infancy, maturation of the brain proceeds at a rapid rate; if injury to the brain occurs, its subsequent development will be correspondingly checked. After such injury, whether from trauma or from disease, the size of the head may remain substandard. Likewise, if a part of the cranial contents are abnormal, as with hydrocephalus, subdural hematoma or tumor, the size of the head may be increased. During the early months of life it is easier to detect intracranial anomalies through abnormality of head measurement than through observation of the infant's achievement level. The examiner's eye serves as a poor gage of the actual or the relative head size, and one's unsupported visual impression should not be given credence. The comparison of head size with chest girth is similarly inadequate.

Additional types of measurements are called for on occasion, notably when shortening of limbs is present or suspected, as in cretinism or dyschondroplasia. In general, however, the aforementioned three measurements suffice for clinical purposes.

With the help of Dr. Meredith, charts were prepared and employed for the graphic portrayal of height and weight in infants and children. These charts were published.[3] More recently, a modification of the infants' growth chart was developed, with inclusion of Meredith's standards for head size.[4] The record form facilitates the plotting and cross comparison of values for measurements and their appraisal in terms of the degree of deviation commonly encountered in normal infants. The forms employed are shown in the accompanying illustrations (charts 1 and 2). Separate charts are used for male and female infants. The uppermost, middle and lowermost sets of curves on each record form relate respectively to the standard values for length, weight and circumference of the head. Each set of reference curves comprises the average (the mean for length and head size, the median value for weight) and

3. Jackson, R. L., and Kelly, H. G.: Growth Charts for Use in Pediatric Practice, J. Pediat. **27**:215 (Sept.) 1945.

4. Meredith, H. V.: Physical Growth from Birth to Two Years: II. Head Circumference, Child Development **17**:1, 1946

also the zone encompassed by approximately two thirds of the measurements observed in the subject population from whom the data were derived.

Simple yet accurate technics of measurement should be used. For the measurement of body length, it is convenient to have a suitable scale (a yardstick or a meter stick) embedded in the top of the examining table. A bracket-like headpiece should project vertically from the zero point of the scale. A movable footpiece should be provided, with a horizontal portion which can slide along the table top and a vertical portion to be placed against the soles of the infant's feet. When making a measurement, the crown of the infant's head should be held in contact with the headpiece, with the chin neither raised nor depressed. The spine should be straight and parallel with the scale, with the legs held in a fully extended position; a preliminary elevation of the hips as the legs are being extended aids in proper alinement. The footpiece then is pushed firmly against the soles until the feet are at right angles with the legs, and the scale is read at the point where the forward edge of the footpiece intersects it.

Head size is measured around the greatest circumference, preferably with a steel tape applied under moderate tension. The value should be recorded to the nearest millimeter. English units to the nearest one fourth of an inch, although adequate for body length, are too gross for determination of head size. The chart, however, permits the recording in either system of units, with direct translation from one to the other.

The date of birth should appear on each record. At the time of each measurement the exact age in months and days should be calculated from the date of birth, and the extra days expressed as a fraction of a month. A dot may be placed on the base line of the chart on the age scale to indicate the current age. The observed values for the three measurements may be indicated similarly by dots in the proper scales on the right margin of the record form. If corresponding dots are made also on the left marginal scales, a ruler may be placed so as to intersect each pair of dots; then the point of intersection of that horizontal level with the age meridian can be seen readily and the value recorded graphically in its proper position (chart 2). A simpler procedure calls for the permanent attachment of a straightedge, so as to project above the table level at the right hand edge of the examining table or desk. The values need be indicated by dots only in the right marginal scales. The right margin of the record form is placed adjacent to the straightedge; a transparent right-angled triangle is then placed in contact with the straightedge. With the horizontal limb of the triangle as a guide, it is easy to project the horizontal position of each measurement value to the proper age meridian.

Clinically these charts have proved useful and simple in application. Well fed, healthy infants of average weight at birth tended to be as

tall as or taller than the value predicted from the average curve, and their weight was in agreement. Not infrequently the thriving infant's measurements corresponded with those of the average infant several weeks older. Conversely, infants of normal weight at birth whose measurements failed to approximate the normal standards generally were those whose total food intake was substandard, or who had disease. Well nourished infants who were immature at the time of birth tended to catch up with the average measurements for their chronologic age. With suitable feeding practices, weight tended to parallel length regardless of the actual length. It has been easy from the graphs to compare the nature and the degree of deviations for any of the three measurements, so as to determine whether the deviations were roughly symmetric for all measurements or whether they were peculiar to themselves.

After molding of the head was corrected, head measurements for any given age tended to fall within the limits indicated on the chart, except for the infant whose body length was notably different from the standard value. With infants who were short because of immaturity at the time of birth, the head tended to be similarly small. With a normally growing central nervous system, however, the trend for growth of the head was stronger and less easily decelerated than for growth in length; hence in the ill favored infant the size of the head may be in accordance with the group average for its age even though its body length is substandard. With infants with nonstandard length for age it is better to determine the average circumference of the head in terms of the observed length and to use that value rather than the chronologic standard as a basis for comparison. To determine the average head size for a given body length, project a horizontal line through the plotted value for observed body length, and at the point where it intersects the midline of the standard curve for length drop a vertical line until it intersects the midline in the standard curve for head size (chart 2). When the observed head measurement falls outside the zone indicated on the record form for the corresponding body length, suspicion of abnormality should be entertained. The relation of aberrant head measurements to clinical diagnoses will be discussed elsewhere.[5]

5. Boyd, J. D.: Unpublished data. In an earlier publication a formula was offered as a means for estimation of the predicted head size in terms of body length. It was expressed as follows: Hd = 0.5L + 10, in which Hd refers to circumference of the head and L to body length, each expressed in centimeters; 10 was an empirically derived constant. When head size was calculated for various body lengths ranging from 50 to 75 cm. and the values were plotted on the record form, it became evident that the constant 10 is too great for the longer infant. If, however, for body lengths of 50 to 65 cm., 65 to 70 cm. and 70 to 75 cm. the constant of 10, 9 or 8½, respectively, is employed, the plotted curve will agree closely with the average head measurement in terms of age; moreover, a range of —1 to +1 cm. will encompass fairly well the range of

It is interesting to compare the standard curves for growth of male and of female infants (charts 1 and 2). In terms of age, the boys tend to be the larger in each of the measurements under consideration, and this difference becomes progressively greater for the "standard" infant throughout the first twelve months. The difference is not great, however, and the average value for each sex falls within the zone of normal variability for the other at each successive month of age. Probably this difference relates more to the initial dimensions at the time of birth than to subsequent variation due to sex. In chart 1 the curves for growth for girls have been superimposed on those for boys in such a manner that a common length at birth is assumed; the girls' curves are indicated by the dotted lines. Such consideration lessens the span between the values for the two sexes; for head size the difference is reduced to a point of minor consideration. The curves for growth for many male and female infants would be essentially identical. The greater constancy in head measurement than in the other body dimensions lends weight to the belief that the rate of growth of the brain is more fundamental and less easily altered than the rate of growth of the body as a whole. Body weight, of course, is subject to wide variability dependent on factors related to nutrition and disease. Such factors also will tend to depress growth in length more than growth in head size, if the brain tissues are normal. Thus, one may expect greater constancy in the pattern of increase for head size than in that for body length. Nevertheless, because of individual variability in size of infants at birth, the body length serves as a better index of predicted head size during infancy than does the infant's chronologic age.

SUMMARY

Record forms are presented as an aid in the graphic recording and appraisal of growth in infants in regard to length, weight and head size. The standard values used for reference were derived from published measurements of infants living under acceptably good environmental conditions; hence they provide a better scale for comparison of growth propensities than a nonselected infant population. The reference curves indicate the average values to be expected at successive age levels throughout infancy and also the range of values observed for approximately two thirds of the subjects from whom the measurements were derived.

Department of Pediatrics .

from —1 to +1 standard deviations as pictured on the record form. (Boyd, J. D.: Clinical Appraisal of Infant's Head Size, Am. J. Dis. Child. **69**:71 [Feb.] 1945.)

Dr. Howard V. Meredith advised in the preparation of the record forms and of this report.

TREATMENT OF SCARLET FEVER

A Comparison of Gamma Globulin with Other Therapeutic Agents in 1,667 Cases

JOHN F. LANDON, M.D.
NEW YORK
AND
LIEUTENANT COMMANDER STANLEY J. JACKSON
UNITED STATES PUBLIC HEALTH SERVICE (R)

PURPOSE OF STUDY

THIS STUDY is an analysis of 1,667 cases of scarlet fever observed over a period of fifteen months (April 1944 to June 1945), 466 cases in a civilian hospital for communicable diseases (Willard Parker Hospital, New York) and 1,201 cases in the contagious disease unit of an institution under military control (United States Public Health Service, Sheepshead Bay, N. Y.). The object is to evaluate the effects of gamma globulin as compared with the effects of four other therapeutic agents in scarlet fever—sulfadiazine, human scarlet fever immune serum, scarlet fever streptococcus antitoxin and symptomatic therapy only.

Gamma globulin,[1] which is the immune globulin fraction of pooled human plasma, is best known at present because of its established worth in the prophylaxis of measles. Other clinical uses for this biologic preparation have been indicated through extensive laboratory investigations and have been the subject of intensive study in the hands of a number of clinicians.[2] It was hoped that gamma globulin might prove to be an ef-

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1. The material used in this study has been prepared from blood collected by the American Red Cross under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. The study was supervised by Dr. C. A. Janeway under the direction of Dr. A. R. Dochez, neither of whom, however, are necessarily responsible for the opinions expressed in this paper.

2. Janeway, C. A.: Clinical Use of Products of Human Fractionation, J. A. M. A. **126**:674-680 (Nov. 11) 1944. Stokes, J., Jr.; Maris, E. P., and Gellis, S. S.: The Use of Concentrated Normal Human Serum Gamma-Globulin (Human Immune Serum Globulin) in the Prophylaxis and Treatment of Measles, J. Clin. Investigation **23**:531-541 (July) 1944. Stokes, J., Jr., and Neefe, J. R.: The Prevention and Alleviation of Infectious Hepatitis by Gamma-Globulin: Preliminary Note, J. A. M. A. **127**:144-145 (Jan. 20) 1945. Havens, W. P., Jr., and Paul J. R.: Prevention of Infectious Hepatitis with Gamma-Globulin, ibid. **129**:270-272

fective agent in the control of diseases of streptococcic origin; consequently scarlet fever was selected as a representative of this group for initial study.

The fractionation process devised by Cohn, Oncley, Strong, Hughes and Armstrong[3] has made it possible to concentrate the gamma-globulin fraction (which is known to contain most, if not all, the immune substances of normal human blood) to such an extent that it contains approximately three to five times as high a titer of scarlet fever streptococcus antitoxin as the average pool of human scarlet fever immune serum,[4] the prophylactic and therapeutic use of which has been favorably reported on by a number of observers.[5] In the preparations used in this study, gamma globulin was concentrated twenty-five times and the scarlatinal antitoxin titers varied from 35 to 80 neutralizing units. (That is, each cubic centimeter would neutralize 1,750 to 4,000 skin test doses of scarlet fever toxin.) It is probable that gamma globulin contains those antibacterial antibodies present in normal adult blood, although there is little evidence for this statement from present laboratory tests. Unfortunately, at present, it can be employed only intramuscularly. Although its intravenous use is contraindicated because of severe reactions encountered in certain patients, its intramuscular use as described in this paper has proved entirely safe.

METHOD OF STUDY

It has seemed advisable to analyze the data from the two services separately because of the considerable divergence in the types of patients studied and in the methods used in caring for them. The main differences may be enumerated as follows:

1. At Sheepshead Bay the previous health and general nutrition of the patients were excellent. For the most part they consisted of trainees from all parts of the country recently inducted into the service after several rigid physical examinations. These trainees were housed in barracks employing the tier bunk system, and all were trained in groups; both of these factors permitted rather close person to person contact.

(Sept. 22) 1945. Janeway, C. A.: Use of Concentrated Human Serum γ Gamma-Globulin in the Prevention and Attenuation of Measles, Bull. New York Acad. Med. **21**:202-222 (April) 1945.

3. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.: The Characterization of the Protein Factions of Human Plasma, J. Clin. Investigation **23**:417-432 (July) 1944.

4. Enders, J. F.: The Concentrations of Certain Antibodies in Globulin Fractions Derived from Human Blood Plasma, J. Clin. Investigation **23**:510-530 (July) 1944.

5. Hoyne, A. L.; Levinson, S. O., and Thalhimer, W.: Convalescent Scarlet Fever Serum, J. A. M. A. **105**:783-789 (Sept.) 1935.

At Willard Parker Hospital the patients were drawn primarily from homes of underprivileged parents scattered throughout Manhattan and Bronx, from other semiprivate and city hospitals and from child-caring institutions in greater Manhattan. In comparison with Sheepshead Bay it may be stated that the previous health and nutrition of the patients at Willard Parker Hospital were inferior.

2. At Sheepshead Bay the average age of the trainees was between 18 and 19 years, whereas the average age of patients treated at Willard Parker Hospital was between 7 and 8 years.

3. The patients at Sheepshead Bay were hospitalized in open wards with no segregation of patients; on the other hand, at Willard Parker Hospital rigid individual isolation technic was practiced, the patients being cared for either in separate rooms or in cubicled wards.

Cases were classified as "severe" and "mild," all those in which the patient had a temperature of 102 F. or over or in which he evidenced a marked toxemia on admission being considered as "severe." At the Willard Parker Hospital, because it seemed administratively unwise to withhold some form of specific therapy, even though on trial, from patients with "severe" cases, it was decided to treat those patients with gamma globulin and scarlet fever streptococcus antitoxin for comparison. However, in the "mild" cases it was felt justified to withhold "specific" therapy in alternate cases, since other than symptomatic treatment as a rule was not employed in such cases. On the other hand, at Sheepshead Bay in 68 cases graded as "severe" the patients received symptomatic treatment only. The considerable divergence in the number of patients treated by various methods at the Sheepshead Bay Hospital is accounted for by fact that during epidemics the size of the service necessitated assignment of more than one medical officer and each officer chose his own method of treatment.

The criteria for the results of treatment were (1) immediate effect on constitutional signs and symptoms, (2) effect on prevention of early septic complications and (3) effect on prevention of late nonsuppurative complications.

Dosage.—Since the optimum dose of gamma globulin in the treatment of scarlet fever has not yet been established, it was suggested that 40 cc. be given intramuscularly. This represented from 1,400 to 3,200 units of antitoxin in different preparations. Such dosage was occasionally modified according to extremes of weight. Scarlet fever streptococcus antitoxin[6] was administered in doses of either 9,000 units or 27,000 units since some authorities are of the opinion that the former dosage is not adequate. It was also administered intramuscularly following the usual

6. The preparation employed was Lederle's antitoxin, refined and concentrated by enzyme digestion.

test for horse serum sensitivity. At Sheepshead Bay human scarlet fever immune serum was administered intravenously in doses from 60 to 120 cc.; sulfadiazine was given routinely in doses of 3 Gm. initially followed by 1 Gm. every four hours.

Collection of Data.—The data were transcribed daily on special forms for subsequent analysis. At the Willard Parker Hospital weekly conferences were held for discussion of the value of the material in each individual case and to insure a clearly uniform understanding of the terminology employed, since considerable difficulty was encountered in the interpretations of terms such as cervical adenitis and otitis media. In general, only routine laboratory procedures were performed, special tests being performed and recorded only as indicated.

Diagnostic Criteria.—In the very mild type of scarlet fever difficulty in establishing an accurate diagnosis is sometimes encountered. Consequently any case presenting an eruption but with throat cultures negative for beta hemolytic streptococcus was excluded unless repeat cultures showed the presence of the organism. Dick and Schultz-Charlton tests were performed only occasionally.

Through the courtesy of Dr. R. C. Lancefield of the Hospital of the Rockefeller Institute for Medical Research, forty-two throat cultures and four sputum cultures were studied for type in this series. Eight different types of group A hemolytic streptococci were recovered but the predominant types were 30 (47 per cent) and 17 (22 per cent).

RESULTS

Interest centered on two main problems—first, the initial effect of the material employed which was measured as accurately as possible, by the degree and rapidity of subsidence of fever, sore throat, evidences of toxemia (nausea, vomiting, prostration and disappearance of the rash). Second, and probably of greater importance, was an estimation of the effect of the various agents in preventing complications, both early (septic, e.g. otitis media, sinusitis and cervical adenitis) and late (rheumatic fever and nephritis).

Initial Effect of Gamma Globulin in Severe Cases.—One hundred and three patients with severe cases received gamma globulin at Willard Parker Hospital and 135 at Sheepshead Bay. In the great majority of patients treated with gamma globulin, with the exception of those in whom complications developed, the temperature fell to normal within forty-eight hours and remained normal. The rash also faded rapidly and subjective symptoms with the exception of sore throat markedly abated within forty-eight hours. Except for occasional soreness at the site of injection, no local reactions were noted and no general reactions were ob-

served. Controls for the "severe" cases at Willard Parker Hospital consisted of 81 patients receiving scarlet fever streptococus antitoxin alternating with globulin were graded as excellent or good in 63 per cent of the severe cases at the Willard Parker Hosiptal and in 89 per cent of such cases at Sheepshead Bay. The results of treatment with antitoxin in severe cases, however, were graded at only 45 per cent as excellent or good. The difference between 63 per cent good results in the severe cases with gamma globulin and 45 per cent with antitoxin is considered statistically significant. In addition, in a large percentage (79 per cent) of the antitoxin-treated patients there was a postcritical rise in temperature about the sixth day after injection without symptomatic effect on the patient (charts 1 and 2). No general difference in results was noted between patients receiving 9,000 units of antitoxin as compared with those receiving 27,000 units. Frank serum sickness did not develop in any case.

TABLE 1.—*Evaluation of Initial Effects*

	Willard Parker Hospital			Sheepshead Bay	
	Severe		Mild	Severe	Mild
	Gamma Globulin	Anti-toxin	Gamma Globulin	Gamma Globulin	Gamma Globulin
Excellent	48	20	31	94	12
Good	17	16	32	27	6
Fair	16	20	20	2	4
No Result	22	25	18	12	2
Total	103	81	101	135	24
% Excellent or Good	63	45	62	89	75

One hundred and one patients with mild cases also received gamma globulin at Willard Parker Hospital and 24 at Sheepshead Bay. Of these 62 per cent at Willard Parker Hospital and 75 per cent at Sheepshead Bay were rated as showing an excellent or good result.

However, there were 12 cases in which antitoxin could not be administered because of cutaneous or ocular sensitivity to horse serum.

Early Complications.—In the early portion of this study (winter and spring, 1944) at the Willard Parker Hospital, controls consisted of 98 (symptomatic group 1) cases not strictly alternating with "mild" cases in which gamma globulin was given, but occurring during the same period of time; later (fall 1944 and spring 1945) 83 (symptomatic group 2) strictly alternate cases were studied.

The incidence of early complications under various modes of treatment in both mild and severe cases at both institutions is shown in table 2. It will be noted that in only 2 per cent of those with mild cases receiving gamma globulin at Willard Parker Hospital complications developed (1 case of catarrhal otitis media and 1 case of sinusitis) whereas

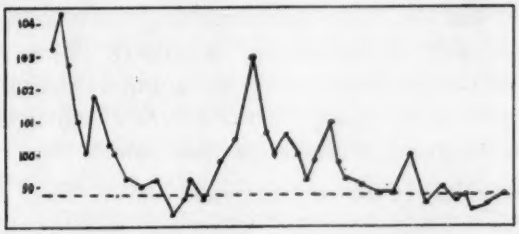

Chart 1.—Typical reaction to antitoxin.

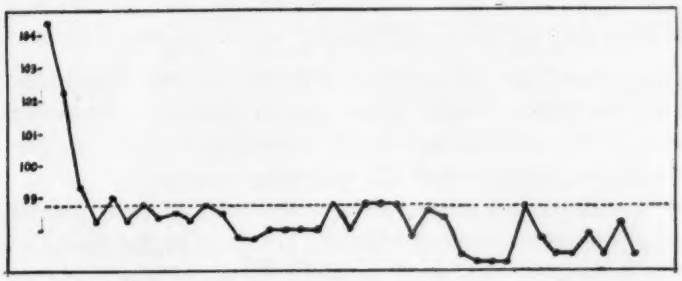

Chart 2.—Typical reaction to gamma globulin.

TABLE 2.—*Incidence of Early Complications*

Type of Treatment	No. of Cases	With Septic Complications	
	Mild Cases	No.	Per Cent
Willard Parker Hospital (466 Cases)			
Gamma globulin	101	2	2
Symptomatic group 1	98	9	9.2
Symptomatic group 2	83	15	18.1
	Severe Cases		
Gamma globulin	103	14	13.6
Antitoxin	81	10	12.3
Sheepshead Bay (Marine) Hospital (1,201 Cases)			
	Mild Cases		
Gamma globulin	24	2	8.3
Symptomatic	267	63	23.5
Sulfadiazine	292	51	17.4
Convalescent serum	64	15	23.4
	Severe Cases		
Gamma globulin	135	24	17.8
Symptomatic	68	25	36.7
Sulfadiazine	174	39	22.4
Convalescent serum	177	45	25.4

in 8.2 per cent and 18.1 per cent respectively in the symptomatically treated groups early complications developed. This is considered significant. The complication rate in the group of patients with severe cases treated with antitoxin at Willard Parker Hospital was essentially the same as in the group receiving gamma globulin.

At Sheepshead Bay 24 patients with mild cases received gamma globulin with increased doses (discussed later) and are compared with 292 receiving sulfadiazine, 64 receiving convalescent serum and 267 treated symptomatically. The comparative percentage of early complications would appear to favor gamma globulin, but the number of cases is too small to have any statistical significance when considered alone.

At Sheepshead Bay 135 patients with severe cases (including 28 receiving increased doses) were given gamma globulin. These were compared with 68 treated symptomatically (acetylsalicylic acid, gargles, etc.), 174 receiving sulfadiazine and 177 receiving convalescent serum. It will be noted that in the group with severe cases twice as many complications occurred in the symptomatically treated group as in the group receiving gamma globuin. The difference between the latter group and those receiving sulfadiazine or convalescent serum was not as marked. The average day on which septic complications occurred was the seventh day after treatment was started.

A special study of 52 severe and mild cases at Sheepshead Bay already included in the general analysis was made from the angle of increased dosage of gamma globulin. These patients received 40 cc. of gamma globulin on admission and 20 cc. on the day of discharge. These were compared with 63 cases occurring concurrently in which only symptomatic treatment was employed. Although the number of patients is small, it seems worthy of note that in 40 per cent of the patients treated symptomatically complications developed as compared with 15 per cent in the group treated with gamma globulin. Furthermore, no patient receiving an additional dose of gamma globulin was readmitted to the hospital suffering from any complication whereas in the 63 patients in the symptomatically treated group complications ensued in 4 (2 cases of streptococcic pneumonia and 2 cases of rheumatic fever) necessitating readmission.

In reviewing the significance of the presented data, Dr. John W. Fertig, professor in biostatistics in the School of Public Health, Columbia University, comments:

> There are thus three comparisons in which the percentage for gamma-globulin cases is less than that for the symptomatically treated cases, mild or severe. Two of these comparisons are in themselves significant, and the other is almost so. It thus appears certain that the use of gamma-globulin cuts down the incidence of early complications, as compared with the symptomatic treatment.

Late Complications.—Diagnostic Criteria: The convalescent care program and the excellent unit record system at Sheepshead Bay made it almost certain that any case in which a complication developed within a two month period would be on file.

At the Willard Parker Hospital follow-up one to two years after discharge from the hospital was accomplished by means of a card system with personal investigation in all cases in which any illness was reported subsequent to discharge from the hospital. This was approximately 45 per cent effective (of 466 cases, 209 were accurately followed up).

TABLE 3.—*Early Complications*
Severe Cases at Willard Parker Hospital

Complication	Gamma-Globulin	Antitoxin
Otitis media	9	3
Adenitis	3	4
Sinusitis	1	1
Tonsillitis	1	
Pneumonia		1
Peritonsillar abscess		1
	14	10

Severe Cases at Sheepshead Bay Hospital (554)

Complication	Gamma Globulin	Symptomatic	Sulfadiazine	Convalescent Serum
Otitis media		8	17	18
Adenitis	2	5	6	3
Sinusitis	15	7	9	12
Pneumonia	3	2	4	9
Peritonsillar abscess		1		1
Laryngitis	3	1	3	1
Strep. dermatitis	1	1		1
	24	25	39	45

In the case of acute rheumatic fever at Sheepshead Bay the diagnosis was made on the basis of a careful history, physical examination, erythrocyte sedimentation rate, white blood count and electrocardiographic findings. These studies were performed in all suspected cases. The erythrocyte sedimentation rate and electrocardiograms were taken on the average of once every two weeks. All these patients were treated with salicylate therapy and local supportive measures. A great deal of emphasis was placed on the erythrocyte sedimentation rate as a guide to diagnosis and disposition of the case. As a rule, all patients were retained in the hospital until they had a normal erythrocyte sedimentation rate and

electrocardiographic findings. In a few instances, as a result of the irreparable cardiac damage, patients were discharged from the hospital with abnormal electrocardiograms. Those patients who had persistent abnormalities in the electrocardiogram or other evidences of cardiac involvement were given medical discharges from the service. In the vast majority of cases the laboratory data returned to normal and the physical examination eventually gave negative results. These patients were then placed on light duty (convalescent duty) for periods varying from one to two months. At the end of that time they returned to the cardiac clinic for reexamination and a revaluation of their condition. If they were normal at that time they were allowed to proceed with regular activities.

Polyarthralgia, occurring in the first week of the disease in a few cases, did not fulfil any of the aforementioned diagnostic criteria and was consequently not classified as a complication.

TABLE 4.—*Incidence of Late Complications*

	Severe Cases, Treatment			Mild Cases, Treatment			
	Symptomatic	Sulfadiazine	Human Scarlet Fever Immune Serum	Symptomatic	Sulfadiazine	Human Scarlet Fever Immune Serum	Total
Rheumatic fever	2	2	4	3	9	—	20
Glomerulonephritis	1	1	1	2	2	—	7
Total	3	3	5	5	11	0	27
No. of cases in group	68	174	177	267	292	64	1042

The diagnosis of acute glomerulonephritis was made only after repeated blood and urinary studies plus the usual clinical findings. The sporadic finding of a trace of albumin and an occaisonal red blood cell was disregarded.

Results.—Among the 135 patients with severe cases treated with gamma globulin and the 24 with mild cases receiving this therapeutic agent at Sheepshead Bay, no late complications developed. However, among the other groups there were twenty-seven late complications as listed in table 4.

To quote Dr. Fertig again:

> The occurrence of no late complications in 135 severe gamma-globulin cases compared with 11 in 419 other severe cases is not definitely significant. Also, the fact that no late complications occurred in 24 mild cases treated with gamma-globulin, whereas there were 16 in 623 other mild cases treated differently, is not significant. Both comparisons considered together, however, do suggest that the incidence of late complications is less with the use of gamma-globulin. Additional support of this statement is furnished by the fact that in 209 cases followed up at the Willard Parker Hospital one to two years after the patient's discharge there were no late complications in 89 cases where gamma-globulin was administered

but 2 cases of definite rheumatic fever had developed in 120 patients receiving other forms of treatment subsequent to the acute illness. It should be emphasized, however, that the 209 cases followed up at Willard Parker represent only 45 per cent of the 466 cases treated at that institution.

DEATHS

Three deaths occurred among 1,201 cases at Sheepshead Bay, an incidence of 0.24 per cent. Descriptions of the course and postmortem findings follow in detail.

Case 1.—A white man, aged 21, was admitted to the U. S. Public Health Service Hospital, Sheepshead Bay, Brooklyn, on May 5, 1944, complaining of a sore throat and a rash of twenty-four hours' duration. Examination revealed the patient to be not acutely ill. The temperature was 101.5 F. The throat was fiery red, and there was a 1 plus scarlatiniform rash. Culture of the throat revealed pure beta hemolytic streptococcus. On the third hospital day sulfadiazine therapy was started, and on the fourth hospital day purulent otitis media developed on the left side and persisted for four days. The use of sulfadiazine was discontinued after eight days and the patient discharged on the fourteenth day, after being asymptomatic for one week.

He was readmitted to the hospital on May 26, with a recurrence of purulent otitis media on the left side. He complained of numbness of the face, hands and feet; headache, nausea, diplopia and vertigo. Examination revealed the patient to be critically ill. Left-sided convulsions were present, and the patient was semicomatose. Neurologic examination revealed evidence of an abscess in the right frontal lobe. He was treated with sulfadiazine intravenously and 200,000 to 300,000 units of penicillin intramuscularly daily. The patient's condition rapidly became worse, and he died on May 31. Postmortem examination revealed abscess of the right frontal lobe and purulent otitis media on the left, due to beta hemolytic streptococcus.

Case 2.—A white man, aged 21, was admitted to the hospital on Dec. 20, 1944 with a history of sore throat, chills, fever and emesis, three to four times a day for two days. Rash appeared on December 20. Examination revealed the patient to be moderately ill. The temperature was 104 F., the pulse rate 120. Symptoms present were rated thus: toxemia 3 plus, rash 3 plus, sore throat 3 plus and gastrointestinal symptoms 2 plus. Many rales were head over the lower part of left lung and a roentgenogram revealed pneumonia in the lower half of this lung. Laboratory data on admission were: white blood cells 17,200; urine albumin (10 mg.). Throat culture revealed pure beta hemolytic streptococcus. At the time of admission the patient was given 50 cc. of human scarlet fever immune serum and 1,000 cc. of 5 per cent dextrose in isotonic sodium chloride solution intravenously. He showed no response to the serum within the first twenty-four hours and continued to complain of sore throat and emesis. The temperature went up to 104.8 F. and the pulse rate to 140. Administration of penicillin was started on December 21 (second day) and continued for six days. It was discontinued after the patient felt fairly well for four days. The temperature was normal for three days. He remained ambulant and felt fairly well with minimal thoracic signs until December 30, at which time he began to complain of pain in the left side of the chest. On that date he suddenly became acutely ill. Examination revealed signs of increasing pneumonia and fluid in the left pleural cavity. In spite of penicillin and supportive therapy, the patient's condition rapidly be-

came worse, and he died on December 30, at 6:30 p.m. Autopsy revealed: lobar pneumonia, left lower lobe, due to beta hemolytic streptococcus, and streptococcic empyema on the left side; swelling and toxic degeneration of all viscera.

CASE 3.—A white youth, aged 19, had a sore throat on Feb. 22, 1945 and a rash on February 23, at which time he was admitted to the hospital. The patient was ambulant and not acutely ill. He had sore throat (2 plus), rash (2 plus) and general toxicity (1 plus). His temperature was 101.7 F. On Febraury 24 he was given 120 cc. of human scarlet fever immune serum intravenously and within twenty-four hours he became asymptomatic. On March 2 and 4 his temperature spiked to 104 F., but he felt fairly well except for a slight sore throat, and examination revealed nasal congestion and a fiery red throat. At this time administration of sulfadiazine and penicillin (250,000 to 300,000 units daily) was started, with a fall in temperature to 101.5. On March 7, the patient suddenly became critically ill, and examination revealed signs of meningitis. In spite of penicillin given intramuscularly, sulfadiazine intravenously and 50,000 unts of penicillin intrathecally, the patient's condition rapidly became worse, and he died on March 8. Postmortem examination revealed a beta hemolytic streptococcic meningitis and an acute purulent sphenoid sinusitis due to beta hemolytic streptococcus.

SUMMARY

One thousand, six hundred and sixty-seven cases of scarlet fever from a civilian and a military hospital have been collected and analyzed.

In 363 cases the immediate effect of gamma globulin in doses of 40 cc. and containing a general average of 1,800 antitoxin units, administered intramuscularly, in reducing fever and toxemia and in alleviating subjective symptoms has been generally satisfactory.

In 81 cases scarlet fever streptococcus antitoxin in doses of 9,000 units and 27,000 units had a favorable effect on the initial signs and symptoms of the disease. However, employment of this preparation was followed by a considerable percentage of postcritical rises in temperature on the sixth to the eighth day after infection, unexplained except on the probable basis of a serum reaction. Despite the great improvement in the refinement of antitoxin, the possibility of sensitization to horse serum must be recognized. Antitoxin has the advantage over gamma globulin in that a smaller amount of material is injected.

In the severe cases the percentage of septic complications was approximately the same whether the patients were treated with globulin or with antitoxin.

Approximately twice as many septic complications occurred in patients with severe cases symptomatically treated as in those receiving gamma globulin.

In 135 patients with severe cases receiving gamma globulin at Sheepshead Bay no late complications developed, whereas 8 cases of rheumatic fever and 3 cases of glomerulonephritis occurred in the 419 patients treated symptomatically or with sulfadiazine or with human scarlet fever immune serum. Furthermore, among 24 patients with mild cases receiving

gamma globulin no late complications developed, whereas in 623 with mild cases receiving other forms of treatment 16 late complications developed.

In a follow-up which was 45 per cent effective at the Willard Parker Hospital one to two years after discharge it was observed that in no patient receiving gamma globulin did a late complication develop, whereas in 1 patient treated with antitoxin and in 1 receiving only symptomatic therapy rheumatic fever developed.

A special group of 52 patients at Sheepshead Bay received an increased dosage of gamma globulin, 20 cc. on discharge in addition to the 40 cc. given initially. Less than one-half as many early complications occurred as in the symptomatically treated control group (63 cases). In the same group no late complications were observed in patients treated with gamma globulin. Two patients with rheumatic fever and 2 with streptococcic pneumonia were readmitted to the hospital, each of whom had received symptomatic treatment only.

In mild cases studied with adequate controls, and from several angles, there was a statistically significant drop in the septic complication rate in patients receiving gamma-globulin as compared with those receiving only symptomatic treatment. The early complication rate of all the "nontreated" patients with mild cases was in fact slightly higher than in those with severe cases receiving gamma globulin or antitoxin.

There were no deaths in the group of 159 patients treated with gamma globulin at Sheepshead Bay, whereas three deaths occurred in a group of 1,042 patients treated in other ways. The deaths are reported in detail. Two of these patients received human scarlet fever immune serum on admission and 1 was given sulfadiazine initially. No deaths occurred at the Willard Parker Hospital in 466 cases.

Local and general reactions with gamma globulin were negligible. No cases of true serum sickness developed following administration of antitoxin, although in a large percentage of those cases an unexplained postcritical rise of temperature developed. Approximately 15 per cent of patients receiving preliminary tests for sensitivity to horse serum were found to give positive reactions.

CONCLUSIONS

1. No entirely reliable specific agent in the treatment of scarlet fever exists at the present time. On the basis of this study, gamma globulin would appear to be the most satisfactory therapeutic agent, both from its immediate effect and from the prevention of early and late complications. Reactions with gamma globulin, either local or general, are negligible. In contrast to animal serums, sensitivity tests are unnecessary, as gamma globulin is a product of human blood.

2. Scarlet fever streptococcus antitoxin also appears to exert a moderately favorable influence on the initial acute phase of the disease and on the development of early septic complications. There is no evidence that this agent prevents late complications. Moreover, the possible danger of sensitization to horse serum as suggested by frequent unexplained rises in temperature must be borne in mind. Furthermore, in a fair percentage of patients the horse serum preparations could not be employed because of positive sensitivity reactions.

3. The relative lack of satisfactory statistical evidence of the efficacy of gamma globulin in preventing septic complications in the severe cases but its consistent success in so doing in the mild cases suggests that the dose used (40 cc.) in the severe cases is inadequate and should either be initially increased quantitatively or qualitatively or be supplemented by a "boosting" dose five to seven days after the initial injection at about the time when septic complications are most prone to occur. Trial of a gamma globulin fraction from human scarlet fever immune serum should be illuminating and the possibility of eventually giving gamma globulin intravenously should be borne in mind.

4. The high percentage of complications occurring in patients with "mild" cases symptomatically treated suggests that this clinically undramatic, relatively nontoxic form of the disease is not innocuous from the point of view of development of complications with subsequent development of rheumatic fever or nephritis. If the results from the data here presented are corroborated, it seems probable that every patient with scarlet fever should receive some form of "specific" therapy, regardless of severity.

5. This study suggests the possibility that gamma globulin used in the treatment of scarlet fever may be effective in lowering the incidence of both early and late complications, especially rheumatic fever. Further studies on the value of this agent as compared to penicillin and antitoxin in the therapeusis of scarlet fever are at present being conducted.

ATTEMPTS TO ADAPT PRUNUS VIRUS I TO COTTON RATS AND MONKEYS

JOHN A. TOOMEY, M.D.
P. P. PIRONE, M.D.
AND
WILLIAM S. TAKACS, M.D.
CLEVELAND

EPIDEMICS of poliomyelitis usually start about the time fruits and vegetables begin to ripen. This is true not only for epidemics in the north, but also for those in the south temperate zone.[1]

Many patients with poliomyelitis admitted to City Hospital, Cleveland, gave a history of eating fruits just prior to the onset of the disease and often spontaneously connected the eating of fruits with the disease.

One of us (Toomey) has often suggested that the virus which causes the infection could be carried into the gastrointestinal tract either in or on food. He has made numerous, but unsuccessful, attempts to initiate and to propagate the disease in animals by injecting extracts or washings from fruits and vegetables.[2] Peaches are frequently implicated by the laity, and these stone fruits are often infected with viruses. It occurred to us that Prunus virus I (peach yellows), or some other virus in or on infected fruits, migh mutate into poliomyelitis virus when consumed by human beings.

The present series of experiments was conducted chiefly to determine whether Prunus virus I could be acclimated to the cotton rat and produce a recognizable and distinctive disease entity in that animal.

To aid us in collecting virus-infected peaches and to provide information on plant viruses, we obtained the assistance of Prof. P. P. Pirone, associate plant pathologist at Rutgers University. He collected several hundred hard green fruits from trees showing typical symptoms of peach

From the Jack and Heintz Laboratory, Department of Contagious Diseases, City Hospital; The Department of Pediatrics, Western Reserve University, Cleveland, and New Jersey Agricultural Experiment Station, Rutgers University, New Brunswick.

1. Toomey, J. A., and August, M. H.: Poliomyelitis: Comparison Between the Epidemic Peak and Harvest Peak, Am. J. Dis. Child. **46**:262 (Aug.) 1933.

2. Toomey, J. A.; Takacs, W. S., and Tischer, L. A.: Attempts to Recover Poliomyelitis Virus from Fruit, Well Water, Chicken Cords, and Dog Stools, J. Pediat. **23**:168, 1943.

yellows in two New Jersey orchards in August 1946. These trees had shown typical symptoms of the yellow disease during the 1945 season. The fruits referred to as lot no. 1 were collected near Finesville, N. J. on Aug. 12, 1946, those referred to as lot no. 2 were obtained at Chester, N. J., on Aug. 27, 1946.

During 1946 and prior to harvest, the trees had been sprayed with lead arsenate—lime and with wettable sulfur. The former mixture was used early in the season and up to the time the fruits were about ½ inch (1.27 cm.) in diameter. The wettable sulfur was applied for at least six weeks before harvest, from approximately weekly to ten day intervals.

The fruits were individually wrapped in wax paper, packed and shipped to Cleveland via air express. Immediately on arrival they were pared and the parings mashed in a Waring blender. The mash was then centrifuged and either the supernate or an eluate from the supernate was injected into cotton rats. Eluates were prepared according to standard methods.[3] All operations, except the actual injections, were conducted in a refrigerator at 4 F. Individual solutions containing 1,000 units of streptomycin and 100 units of penicillin were made up and to each 3 cc. of supernate or eluate 0.03 cc. of each solution was added one hour or more before injection, to prevent bacterial infection.

Hydrocyanide gas odor was detected when the stones were ground, and when leaves were mashed, but there did not seem to be much odor to the skin supernates after a few minutes of exposure.

All injections were made as follows: 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally. The cotton rats used weighed approximately 115 Gm. each. At least 10 animals were used in each of the experiments. In those few in which monkeys were used, deviations from this technic are specifically described.

The supernate, as well as its eluate prepared from the mash of unwashed peaches from green fruit infected with Prunus virus I, was toxic (experiments 1, 2, 8 and 10), although paralysis did not develop in any of the rats. This resulted from the proportions used. A lesser percentage was not toxic. The supernate from parings of washed, virus-infected peaches was not so toxic, but two days had elapsed between preparation and injection, and oxidation may have modified the toxicity. However, the eluted supernate from the washed peaches was as toxic (experiments 11, 12) as the unwashed material.

Not only was the production of paralysis absent, but blind subpassages, using the brains and the cords of the animals that died several days after injection with less toxic doses of eluates, failed to produce any disease condition that bore any semblance to poliomyelitis (experiments

3. Schaeffer, M., and Brebner, W. B.: Purification of Poliomyelitic Virus, Arch. Path. 15:221 (Feb.) 1933.

5, 6 and 7). Specific antiserum added to the original supernate (experiment 16) revealed little, since the material had lost its toxicity.

A Vervet monkey was given 40 cc. of isotonic sodium chloride solution containing a 25 per cent suspension of peach supernate by stomach tube. The material had been made from the peaches used in experiment 1 (lot no. 1) and had been kept fifty-one days on dry ice. This had originally been toxic for cotton rats, but on the fifty-first day it was not toxic when the original dosage was again used. The monkey also received 1 cc. of the supernate subcutaneously.

Three hours later the animal was furred (3:30 p.m.). An amount of supernate similar to the first was given the same way at 4 p.m., followed by an injection of 0.5 cc. of a 1:128 solution of morphine. A third dose, using a similar amount of supernate and a second injection of morphine were administered at 10 a.m. the following day and, in addition, the animal was fed two peaches taken from the same batch from which the supernate and eluate were processed and which had been in the ice box fifty-one days. A subcutaneous injection was not given.

On this day the animal breathed slowly and laboriously. It was furred and weak and could be caught easily. It was then given 30 cc. of a 25 per cent peach mash by stomach tube, some of which was regurgitated It was offered two peaches, but both arms were so weak that they could not hold the fruit. Breathing became difficult and although the animal was alive, it was cold and semicomatose. Respirations slowed to five per minute, and the animal died that morning.

A second Vervet monkey received injections on September 7 with a 10 per cent suspension of the brain and cord obtained from the preceding animal, as follows: 1 cc. intracerebrally, 1 cc. intraperitoneally, 1 cc. subcutaneously and 0.2 cc. instilled into each nostril. The animal was ill from September 7 to September 12. On September 12 it again received injections with the same amounts of 10 per cent brain-cord mixture. On September 13 its condition became worse, and it had tremors in the right arm. These disappeared in twenty-four hours. On September 16 there seemed to be weakness in both hands. It recovered from this condition and was very active by the eighteenth. On September 23, all four extremities seemed to be spastic, probably a Rivers effect.[4] The animal was killed on September 25.

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4. Rivers, T. M.: Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39, 1933. Schwentker, F. F., and Rivers, T. M.: Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, ibid. **60**:559, 1934. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, ibid. **61**:689, 1935.

Grossly, the brain and cord were hyperemic. Sections were taken in the same manner as were those obtained from the first monkey, but the lesions did not resemble those of poliomyelitis.

A blind passage was tried into a third Vervet monkey and a 10 per cent cord and pons suspension of the second animal was injected in the following manner: 1 cc. intracerebrally, 2 cc. subcutaneously and 4 cc.

Reaction of Cotton Rats to Various Types of Suspensions Obtained from the Peach

Experiment	No. Animals		No. Died	No. Paralyzed
1	10	Unwashed virus-infected peach mash supernate (8/17) (lot 1)	10	0
2	10	Eluate from same specimen (exp. 1)	10	0
3	12	Graduated percentages of eluate obtained in exp. 2, range 1 to 100%	5	0
4	10	Graduated per cent of supernate from exp. 1, 5 days between preparation and injection	3	0
5	10	10% brain and cord suspension of an animal in exp. 3 which died on 5th day; no paralysis	0	0
6	10	10% brain cord suspension from 2 rats in exp. 3 which died on 7th and 24th days; no paralysis	3	0
7	10	10% brain and cord suspension of rats in exp. 6 which died on 5th and 7th days	2 (trauma)	0
8	10	Unwashed virus-infected peach mash supernate collected from a different orchard (lot 2)	9	0
9	10	Graduated percentages of supernate used in exp. 8, range 5 to 100%	2	0
10	10	Eluate of supernate from exp. 8	7	0
11	10	Washed virus-infected peach parings, supernate-done two days after preparation	1	0
12	10	Supernate obtained from exp. 11, eluted and injected	8	0
13	10	10% supernate of exp. 1 injected 10/9	1 (trauma)	0
14	10	Eluted supernate of exp. 2; kept on dry ice 51 days, 8/17-10/9	2 (trauma)	0
15	10	Unwashed, uninfected, peach supernate kept on dry ice 51 days	1 (killed)	0
16	10	Original supernate of exp. 1 combined with horse poliomyelitis antiserum	1 (trauma)	0

intraperitoneally, and 0.5 cc. was instilled into each nostril. The animal was slow the next day but showed nothing clinically that could be called paralysis. It was given a second set of injections on October 10, and had a convulsion, probably a reaction similar in nature to that described by Rivers.[4] The monkey recovered and at no time subsequently evinced any evidence of paralysis or other disease.

COMMENT

When pared and exposed to air, peaches, apples and certain other fruits darken as a result of the activity of oxidizing enzymes, and in this

oxidation process Prunus virus I might be destroyed. This could not be too great a factor in the present work, since the specimens were quickly prepared at a relatively low temperature.

The presence of spray residues on the fruits as a factor in toxicity was considered. The only material sprayed on the fruits, six weeks prior to harvest, was sulfur. Sulfur is stable and combines with oxygen only at high temperatures and could not have been lost as it was by refrigeration. The eluted supernate (experiment 2), which was originally toxic, lost its toxicity after storage on dry ice for fifty-one days. The loss of toxicity might be explained on the basis of alteration of the toxic factor by freezing and thawing or oxidation.

SUMMARY

1. Fresh supernates and eluates from green, unripe peaches infected with Prunus virus I were found to be toxic for cotton rats.

2. Attempts to transmit any disease condition from these animals that died resulted in failure.

3. Blind subpassages into subsequent generations of cotton rats also failed.

4. Blind subpassages in a few Vervet monkeys gave negative results.

SIGMOIDOSCOPY IN THE DIAGNOSIS OF ALLERGIC COLITIS

J. H. LAPIN, M.D.
AND
W. W. WEISSBERG, M.D.
NEW YORK

SINCE ANDERSEN'S[1] noteworthy attempts at classification of the diseases comprising the celiac syndrome, it has been possible to individualize dietary and other treatment on a more rational basis. Andersen until recently[2] had classified diseases in the celiac syndrome as (*a*) infantile steatorrhea, (*b*) intolerance of starch, (*b*) celiac disease and (*d*) cystic fibrosis of the pancreas. In 1944, one of us[3] had added a fifth classification—an allergic celiac syndrome. At this time it was pointed out that the high percentage of allergic family histories obtainable in cases of metabolic diarrheas makes the diagnosis of allergic celiac syndrome extremely difficult. Many investigators had postulated that gastrointestinal difficulties may originate in an allergic enterocolitis in which an allergic edema of the gastrointestinal mucosa forms a barrier to the absorption of split fats. Thus, Kunstadter,[4] Riley,[5] and McKhann[6] as well as one of us (J.H.L.)[3] had reported cases in which gastrointestinal allergy produced the celiac type of diarrhea.

From the Pediatrics Service of the Bronx Hospital.

1. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, Am. J. Dis. Child. **56**:344 (Aug.) 1938; (*b*) Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, ibid. **63**:643 (April) 1942. (*c*) Andersen, D. H., and Hodges, R. G.: Celiac Syndrome and Cystic Fibrosis of the Pancreas, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 1, chap. 29.

2. Andersen, D. H.: Celiac Syndrome: VI. The Relationship of Celiac Disease, Starch Intolerance and Steatorrhea, J. Pediat. **30**:564 (May) 1947.

3. Lapin, J. H.: Recurrent and Chronic Diarrhea in Infancy and Childhood, Am. J. Dis. Child. **67**:139 (Feb.) 1944.

4. Kunstadter, R. H.: Gastro-Intestinal Allergy and the Celiac Syndrome, J. Pediat. **21**:193 (Aug.) 1942.

5. Riley, I. D.: Metabolic Eczema in Idiopathic Steatorrhea, Lancet **1**:262 (Feb. 4) 1939.

6. McKhann, C. F.; Spector, S., and Meserve, E. R.: Association of Gastrc Intestinal Allergy with Celiac Syndrome, J. Pediat. **22**:362 (March) 1943.

The term celiac syndrome, as used by Andersen,[2] is applied to patients who have chronic or recurrent diarrhea some time between birth and the sixth year, are intolerant of a normal diet for their age, respond to dietary therapy and at some time in their course have a protuberant abdomen and a slow gain in weight. In somewhat less than half the cases she has found a satisfactory morphologic or bacteriologic explanation, for example: fibrocystic disease of the pancreas, stenosis of the ileum or enteric infection due to Ascaris, Giardia or Salmonella. The condition in the cases in which no anatomic or bacteriologic basis is found is termed idiopathic celiac disease.

The condition in the cases we wish to report is, we feel, common, and the term allergic colitis has been used. These patients usually do not have a protuberant abdomen or atrophy of the buttocks and are relatively well nourished. In severe, or poorly treated allergic colitis, the protuberant abdomen, atrophy of the buttocks and poor nutrition which result would fulfil the requirements for the celiac syndrome on an allergic basis—the so-called allergic celiac syndrome. As will be noted later, there are relatively few cases of allergic colitis severe enough to necessitate hospitalization, but pediatricians see many examples of chronic or recurrent diarrhea with intolerance of a normal diet, with no or a slow gain in weight, and response to appropriate dietary therapy, which prove to be allergic in character.

Objective evidence of this type of case of allergic colitis has been lacking until now. Cutaneous tests, unfortunately, are notoriously unreliable in this age group, from birth to 3 years of age. Amelioration of gastrointestinal symptoms on elimination of a suspected food may indicate allergy to that food, but may also indicate nonallergic inability to digest a given food. Thus, a young child with a true celiac disease can rarely digest potato, but this inability is clearly not on an allergic basis. An allergic family history is often a clue to the cause of a celiac type of diarrhea, but such a history is too frequent to be regarded as proof. The previous or present existence of eczema urticaria or asthma may give the physician a lead, and often failure to respond to a celiac diet is also suggestive. This dilemma is of old standing. Milk is, of course, a common offender, and the old clinicians, without any attempt at etiologic classification, often recommended either plain or evaporated milk boiled four to eight hours. Denaturation of the antigenicity of milk by such measures may explain the good results in some of their cases. Other common offenders are banana and scraped raw apple, which have been standbys in the treatment of other types of celiac disease. The presence of large masses of undigested banana or apple in the stools will often help to confirm a suspicion of the allergic character of a diarrhea.

Sigmoidoscopy in cases of the celiac syndrome has furnished an objective method of judgment of the allergic type of enterocolitis, the so-

called allergic colitis. This has not been reported in the pediatric literature, but Felsen,[7] treating both infants and adults, describes the findings in allergic colitis as follows:

> The mucosa appears reddened, edematous and is covered with considerable mucus. Bleeding is rare, and no visible lymphoid hyperplasia is noted. In some instances, actual localized areas of edema resembling wheals may be noted, with a surrounding zone of marked congestion. The appearance in most cases is not unlike that seen in vasomotor rhinitis. Sigmoidoscopic crypt aspiration wet smear may reveal an occasional eosinophile but no purulent cytology in the exudate. The offending allergen may be bacterial, food or pollen. In infants and children, the condition is generally due to food or bacterial sensitization. Of foods, cow's milk is the most frequent offender. In infections, those of the upper respiratory tract are most often responsible."

Andresen[8] reported that 66 per cent of patients with ulcerative colitis 10 to 51 years of age were allergic to some food, and sigmoidoscopy in early stages showed hyperemia, hypersecretion and mucosal edema of the colon. This seemed identical with the pictures of allergic reactions in the intestinal mucosa produced in sensitization experiments by Walzer and his group[9].

In this paper we reported the use of sigmoidoscopy as furnishing objective evidence of the allergic character of certain cases of chronic and recurrent diarrhea. The sigmoidoscopic picture in cases of cystic fibrosis of the pancreas and in proved cases of celiac disease is completely normal, and will not be reported. We are reporting 3 cases of "allergic colitis."

REPORT OF CASE

Case 1.—P. W., with a family history of allergy on both sides, was first seen at 3 months of age with colic, urticaria and slight diarrhea. On three occasions in the next three months, he had episodes of subfebrile temperature, abdominal colic, hives and slight diarrhea. At 6 months of age he had a slight facial eczema, but did fairly well. He weighed 19 pounds 15 ounces (9,043.5 Gm.) at 10 months of age. At this time, the combination of black, loose, slimy bowel movements and severe abdominal colic forced hospitalization. Examination of stools revealed a moderate amount of undigested starch and normal fat. The black color was explained by large masses of undigested fiber, staining yellow with strong iodine solution, which seemed to be woody fibers from banana. Roentgen examination of the gastrointestinal tract gave negative results. Sigmoidoscopy revealed that the mucous membrane was hyperemic and edematous and covered with considerable mucus. There was no lymphoid hyperplasia or ulceration; on a celiac diet the child lost 9 ounces (255 Gm.) in the next two months. An episode of acute diar-

7. Felsen, J.: (*a*) Intestinal Manifestations of Systemic Disease, Rev. Gastroenterol. **5**:114 (June) 1938.

8. Andresen, A. F. R.: Ulcerative Colitis—Allergic Phenomenon, Am. J. Digest. Dis. **9**:91 (March) 1942.

9. Gray, I.; Harten, M., and Walzer, M.: Studies in Mucous Membrane Hypersensitiveness: Allergic Reaction in Passively Sensitized Mucous Membranes of Ileum and Colon in Humans, Ann. Int. Med. **13**:2050 (May) 1940.

rhea resulted in a change to a high protein diet, which produced abdominal colic and urticaria. The child was then given an evaporated milk formula boiled two hours and "pyribenzamine" (N pyridyl-N benzyl-N-dimethyl ethylenediamine hydrochloride) and has gained one pound (453.59 Gm.) in the last month. Banana appears undigested in the stools, and chicken produces urticaria, but he can digest most other foods.

CASE 2.—M. K., an adopted child with an unknown family history, had diarrhea in the neonatal period, followed by colic, gaseous distention and vomiting of large quantities of milk. She did well on a dried milk formula, until the development of a slight diarrhea at 9 months of age. At 15 months of age, she weighed 31 pounds 12 ounces (14,401.5 Gm.). Diarrhea started, with foul odor and much mucus, which she has had for the last eight months. In this eight month period, she lost 1 pound on a celiac diet. The stools contained a normal amount of fat but a moderate amount of undigested starch. A roentgen examination of the gastrointestinal tract gave negative results. Sigmoidoscopy showed the mucosa to be hyperemic, slightly edematous and covered with a little mucus. Cytologic study of the mucosal exudate revealed that it was normal. On aspiration of the sigmoidoscopic crypt enteric pathogens were not found and wet smear failed to reveal Escherichia histolytica. On milk boiled two hours, an elimination diet procedure and "pyribenzamine," the child has gained 1 pound in the last month.

CASE 3.—C. B. had had slight diarrhea and occasional vomiting since birth but did well until 7 months of age, weighing 18 pounds 10 ounces (8,448 Gm.). At this time, movement of the bowels became frequent and the stools were foul, covered with mucus and occasionally blood streaked. There was no response to a celiac diet, although he weighed 21 pounds 6 ounces (9,695.5 Gm.) at 10 months of age. There was a definitely allergic family history. Examination of stools revealed a normal amount of fat and a moderate amount of undigested starch. Sigmoidoscopic examination showed that the mucosa was edematous, hyperemic and covered with mucus. Aspiration of the crypt showed wet smears, and cytologic examination gave normal results. When given milk boiled two hours, an elimination diet and "pyribenzamine," the infant did well, gaining 18 ounces (510.3 Gm.) in one month.

COMMENT

Andersen in her latest article[2] simplifies the classification of diseases in the celiac syndrome by pointing out that the class called starch intolerance previously is really the basis of the other class called celiac disease, and also evolves a rather complex amylase to trypsin ratio in the duodenal fluid as the diagnostic criterion in cases of celiac disease. Of her 81 patients with the celiac syndrome, 14 had a history of allergy. "Of these, only 2 had normal levels of amylase, and probably do not have celiac disease on the basis of starch intolerance. They may be said to present the celiac syndrome on the basis of gastrointestinal allergy." Unfortunately, she is not cognizant of the value of sigmoidoscopy in the differential diagnosis. She says that in the remaining 67 cases evidence of allergy in the patient has been absent or unconvincing, and the incidence of allergy is not significantly greater than has been estimated for the general population. The objection to this reasoning is that these children are very young (the onset in one third before 6 months, one

third from 6 to 12 months, and 1 to 3 years in the remainder). Frank evidences of allergy such as hay fever, asthma and even urticaria are notoriously infrequent in this age group, but often appear later in life. Evidences of a gastrointestinal allergy may, therefore, appear years before the onset of major allergies, and the absence of major allergies before 3 years of age is not to be considered proof militating against the allergic character of a gastrointestinal disturbance. Her viewpoint that amylase levels, amylase to trypsin ratios in the duodenal fluid and gastric hypochlorhydria are the important criteria of the true celiac disease based on starch intolerance has not as yet been confirmed. It seems perfectly possible that an allergic enterocolitis may disturb the amylase trypsin ratio, and therefore important that sigmoidoscopy be done in every case. She herself says that these tests cannot be used to substantiate the diagnosis in infants under 6 months of age, even though clinical symptoms often appear before this age. We have not been able to perform amylase and trypsin studies in the 3 cases reported here. It is our feeling that in the practice of pediatrics in the office the percentage of cases of the celiac syndrome depending on an allergic element is far higher than Andersen reported for a hospitalized group, since usually only patients with an intractable condition are hospitalized.

It seems to us, therefore, that in sigmoidoscopy, pediatricians have a relatively simple method by which to distinguish allergic colitis and allergic celiac syndrome from celiac disease and from cystic fibrosis of the pancreas. From this viewpoint, a rational therapy for allergic colitis can be outlined. First, an elimination diet should be selected, using first evaporated milk boiled several hours, then evaporated goat's milk, then "nutramigen" (amigen 20 per cent, dextrimaltose 42 per cent, milk fat 18 per cent and arrowroot starch 10 per cent) depending on the strength of the milk intolerance, and adding other foods cautiously. I have found repeated checking of stools for undigested starch and fat of great value. Thus, when large pieces of banana or string beans are eliminated practically undigested, they are probably allergens and should be omitted from the diet. Second, "pyribenzamine" or other antihistamine drugs should be used for palliative relief. Third, prophylaxis should be instituted against infections of the upper respiratory tract in those cases in which infections of this type seem to be the sensitizing factor in relapses of intestinal disease.

NOTE.—These 3 cases are included in a much larger series of cases of gastrointestinal allergy, which will be presented as an exhibit at the November meeting of the American Academy of Pediatrics.

The Sigmoidoscopic examinations in our cases were performed by Dr. J. Felsen.

BENEFICIAL EFFECT OF MEASLES ON NEPHROSIS

Report of Three Cases

EDWARD H. MEIZLIK, M.D.
AND
ANNA-MARY CARPENTER, Ph.D.
PITTSBURGH

SEVERAL REPORTS have been published indicating the beneficial effect of measles on the course of the nephrotic syndrome in children. In this hospital the various types of treatment generally recommended for nephrosis, including use of acacia, plasma and protein hydrolysates together with low salt diet, have given little permanent beneficial effects, in contrast to the gratifying improvement that frequently occurs after an attack of measles. This paper deals with a report of 3 cases in which to date the improvement has been permanent.

Bibliography concerning the association of intercurrent measles and the remission of nephrotic symptoms has recently been reviewed by Blumberg and Cassady,[1] and will not be repeated here. In 2 patients with nephrosis in whom Hutchins and Janeway[2] induced measles experimentally prompt remissions occurred.

REPORT OF CASES

CASE 1.—J. M., a white boy, aged 4 years and 4 months, with generalized edema, was admitted to the Children's Hospital of Pittsburgh to the private service of Dr. H. T. Price on Dec. 24, 1946. The patient had been well until ten days prior to admission, when swelling developed around the eyes, which gradually extended to other parts of the body. At that time he was seen by the family physician, who reported his urine to be "filled with albumin." The child was given a diet with low salt content and ordered to remain in bed. Under this regimen the edema failed to subside, and when vomiting developed admission to the hospital was advised.

Except for occasional attacks of tonsillitis, the past medical history was not significant. The family history was noncontributory.

From the Departments of Pediatrics and Pathology, University of Pittsburgh and Children's Hospital of Pittsburgh.

1. Blumberg, R. W., and Cassady, H. A.: Effects of Measles on the Nephrotic Syndrome, Am. J. Dis. Child. 73:151 (Feb.) 1947.

2. Hutchins, G., and Janeway, C. A.: Observations on the Relationship of Measles and Remissions in the Nephrotic Syndrome, Am. J. Dis. Child. 73:242 (Feb.) 1947.

Physical examination gave negative results, except for generalized edema, mild ascites and an injected throat. The temperature was normal. The blood pressure was 112 mm. of mercury systolic and 80 mm. diastolic.

The hemoglobin content of the blood was 14.5 Gm. per hundred cubic centimeters, the red cells numbered 4,500,000 and the white cells 8,700 with a normal differential count. The urine showed a 4 plus reaction for albumin and an occasional neutrophil. At no time were any red blood cells seen in the urine. Chemical microanalysis of the blood revealed a nonprotein nitrogen content of 35 mg. per hundred cubic centimeters; total serum protein 5.11 Gm., with albumin 1.55 Gm., globulin 3.56 Gm. and cholesterol 495 mg.

The treatment consisted of rest in bed, a high protein and low salt diet, and administration of "lactamin,"[3] two tablespoons three times daily. Penicillin therapy was started on admission because of the injected throat. Under this treatment the patient lost 4 pounds (1.8 Kg.) in weight the first week of his hospital stay with a corresponding reduction of the edema. During the second week, the edema recurred and the urine continued to show heavy albuminuria. On his thirteenth day in the hospital the temperature, which heretofore had been normal, rose to 39.4 C. (103 F.). The child vomited frequently and was listless. On his seventeenth day in the hospital, when a rash became apparent, a diagnosis of measles was made. On the following day the urine became albumin free for the first time; it remained so for the rest of his stay in the hospital. The temperature, which fluctuated between 38.3 C. (101. F.) and 39.4 C. (103 F.), dropped to normal on the twentieth day in the hospital. No accurate check could be made of the urinary output because of involuntary voiding. Clinically, however, the edema gradually improved, with complete disappearance by the twenty-fifth day in the hospital. The patient was eating well and acted like a happy normal child. He was discharged from the hospital on Jan. 25, 1947.

Ten months after the onset of measles, the patient is still well. In this interim he has had chickenpox and several respiratory infections without any recurrence of edema or albuminuria.

The blood chemical findings for this patient are shown in table 1*A*.[4] The effect of "lactamin" therapy is indicated by the increase in the albumin content of the blood after a week's treatment. On May 3, 1947 there was a fall in the total proteins with the onset of a cold. Also, after the discontinuance of "lactamin" for a three month period, beginning May 29, 1947, there was not only a reduction in the total blood proteins but also a decrease in albumin with a corresponding rise in globulin.

Case 2.—A. R., a white girl, aged 3 years, showing moderate generalized edema and ascites, was admitted to the Children's Hospital of Pittsburgh as a private patient of Dr. M. D. Silverberg on Feb. 21, 1947. During the preceding four months the patient had had several transient mild episodes of periorbital swelling. These symptoms became more severe, with development of edema of the ankles and a "swollen abdomen." The family physician was consulted and found the urine "full of albumin." He prescribed a low salt diet and a "liquid diuretic." Because the edema failed to subside, admission to the hospital was advised.

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3. This hydrolysate of lactalbumin was kindly furnished by John Wyeth Company, Philadelphia.

4. Carpenter, A. M.: Dilution of Capillary Blood in the Microanalysis of Protein, Am. J. Clin. Path. **17**:565 (July) 1947.

According to the medical history, no recent infection had been present. In the past the child had had several attacks of acute tonsillitis until a tonsillectomy was performed in August 1946. There was a vague history of "three-day measles" in 1945. The family history was irrelevant.

TABLE 1.—*Chemical Analysis of Blood in Cases* 1 *and* 2

	Date	Gm./100 Cc.			Comment
		Total Protein	Albumin	Globulin	
	12-24-46				Admitted; nephrosis of 10 days' duration
	12-27-46	5.11	1.55	3.56	"Lactamin" therapy begun
	1- 4-47	5.55	2.73	2.82	
	1-10-47				Measles rash
	1-11-47				Trace of albumin in urine
	1-16-47				Urine albumin free
	1-17-47	4.56	2.23	2.33	
A.	1-25-47				Patient discharged Chickenpox at home
Case J. M.	2-15-47	6.97	4.10	2.87	Urine albumin free
	3- 7-47	6.31	4.15	2.16	
	4- 4-47	7.52	4.16	3.36	
	5- 3-47	5.91	4.09	1.82	Infection of upper respiratory tract
	5-29-47	7.02	5.08	1.94	"Lactamin" therapy discontinued
	8- 2-47	5.79	3.61	2.18	
	11- 4-47	6.12	4.42	1.70	
	2-21-47				Admitted; nephrosis of 4 months' duration
	2-25-47	5.93	2.50	3.43	
	2-27-47 to 3- 2-47				"Lactamin" therapy not tolerated; discontinued
	3- 4-47	4.83	1.65	3.18	
	3- 5-47				"Amiprote" therapy; diarrhea; therapy discontinued
B.	3- 7-47				Koplik spots
Case A. R.	3- 8-47				"Essenamine" therapy instituted
	3- 9-47				Measles rash; patient discharged
	4- 1-47	6.19	2.67	3.52	
	5- 2-47	5.87	3.90	1.97	
	5-28-47	7.80	7.62	0.18	"Essenamine" therapy discontinued
	8- 7-47	4.22	3.26	0.96	
	11- 4-47	5.75	3.95	1.80	Infection of upper respiratory tract

Physical examination revealed a well developed, well nourished child with no abnormal findings except generalized edema and ascites. The temperature was normal. The blood pressure was 112 mm. of mercury systolic and 76 mm. diastolic.

Initial blood study revealed 13.2 Gm. of hemoglobin per hundred cubic centimeters, 4,600,000 red blood cells and 11,500 white blood cells with an essentially normal differential count. The urine showed a 4 plus reaction to albumin and no red blood cells. At no time were any red blood cells seen in the urine. Chemical microanalysis of the blood revealed a nonprotein nitrogen content of 32.6 mg. per hundred cubic centimeters; total serum protein 5.93 Gm. with albumin 2.5 Gm., globulin 3.43 Gm. and cholesterol 187 mg.

The treatment in the hospital consisted of rest in bed, a high protein, high vitamin diet and protein hydrolysates. The first hydrolysate prescribed was "lactamin," which the patient frequently refused to take; after a five day trial it was discontinued. This was followed by "amiprote."[5] Almost immedately, this preparation induced severe diarrhea, possibly because of the yeast content. Twenty-four hours later "essenamine"[6] was substituted in a dosage of one teaspoon four times daily; this product has been well tolerated by the patient. On the fourth hospital day no edema was evident. On her ninth day in the hospital generalized edema, anorexia and oliguria again developed. This recurrence of edema was followed in four days by cough, photophobia and an elevation in temperature to 39.2 C. (102.6 F.). These symptoms persisted until the sixteenth day in the hospital when a definite measles rash developed. The next day the patient was removed to her home because contagious diseases were not being treated in the hospital at that time.

Immediately after leaving the hospital the edema completely disappeared, and, except for the measles, the patient appeared entirely well. Daily qualitative tests for albumin by her father, a dentist, revealed a "cloud" persisting in the urine. Twenty days after the onset of the measles rash the urine became albumin free. Subsequent urinalyses have given completely negative results for albumin.

At the present time, eight months after the onset of measles, the child is still well. A mild respiratory infection developed in May, with no recurrence of the nephrosis.

The blood chemical findings are shown in table 1*B*. Three weeks after the onset of the measles rash the total serum proteins had risen to 6.19 Gm. per hundred cubic centimeters, but the reversed albumin-globulin ratio persisted. One month later, May 2, 1947, the albumin-globulin ratio had returned to normal. With continued "essenamine" therapy the globulin values continued to fall, and on May 28, 1947 the albumin-globulin ratio was 40:1. With the withdrawal of "essenamine," the total proteins fell, but the albumin-globulin ratio was not reversed.

The following case was not personally observed by us, but was discovered when one of us (E.H.M.) reviewed the charts of all cases of nephrosis in the Children's Hospital of Pittsburgh during the past twenty years.

Case 3.—First Admission: A. O., a white boy, aged 2 1/3 years, was first admitted to the hospital on July 1, 1943, at the request of the family physician, who had noted puffiness around the eyes and on examination detected albumin in the urine.

The family history was noncontributory. Except for a mild case of chickenpox two months prior to admission, the boy had been well.

5. This product, an enzymic digest of beef, casein, lactalbumin and yeast, was kindly furnished by the U. S. Vitamin Corporation, New York.

6. This product, a hydrolysate of lactalbumin, was kindly furnished by the Frederick Stearns Company, Detroit.

On physical examination the child was well developed and did not appear ill. The only abnormal finding was periorbital edema. The blood pressure was 102 mm. of mercury systolic and 70 mm. diastolic. The temperature was 37 C. (98.6 F.).

Blood studies showed 12.2 Gm. of hemoglobin per hundred cubic centimeters, 4,000,000 red blood cells and 10,200 white blood cells with a normal differential count. The urine gave a 4 plus reaction to albumin and microscopically revealed an occasional granular cast and white blood cell. At no time were any red blood cells seen in the urine. Chemical microanalysis of the blood showed a total serum protein of 4.8 Gm. per hundred cubic centimeters with albumin 0.94 Gm. and globulin 3.8 Gm. The nonprotein nitrogen was 26 mg. and cholesterol 475 mg. per hundred cubic centimeters.

On admission the patient was given a high protein, low salt diet. The edema increased until it was generalized. On the ninth hospital day 250 cc. of plasma was administered. This was followed by a marked diuresis with an accompanying reduction of the edema. The boy was discharged on the fifty-first hospital day, at which time very little edema was present. The urine showed a 2 plus reaction to albumin.

Second Admission: After discharge from the hospital the child again became edematous and nineteen days later, on Sept. 8, 1943, was readmitted. At this time there was marked puffiness of the entire face, slight edema of the extremities and mild ascites. The tonsils were large and injected. The temperature was 37.2 C. (100 F.). The blood pressure was within normal limits.

Blood counts remained normal. The urine showed a 4 plus reaction to albumin and an occasional granular cast and white blood cell. The nonprotein nitrogen of the blood was 36 mg.; the total serum protein 5.5 Gm. with albumin 2.3 Gm. and globulin 3.2 Gm. per hundred cubic centimeters.

Treatment consisted of a high protein diet with low salt content, and "aminoids,[7] one teaspoon three times daily. By the eighteenth day in the hospital there was an increase in edema coincident with an elevation of temperature to 38.4 C. (101.2 F.). The following day the temperature reached 39.4 C. (103 F.) and a typical measles rash developed. The fever subsided three days later, and on the same day the urine was free of albumin for the first time. It remained albumin free for the rest of his stay in the hospital. Immediately after the onset of the measles rash, the edema began to subside and was not evident when the patient was discharged on the thirty-ninth day.

Recent correspondence with Dr. Daniel Blitz of Long Island, N. Y., the present family physician, reveals that there has been no recurrence of edema or albuminuria although the child has had several respiratory infections. At the time this article was written four years after the onset of measles, the patient was apparently cured.

CLINICAL FEATURES

Three patients suffering from nephrosis showed complete remission of symptoms following infection with measles and to date appear cured; in 1 of them there has been no recurrence of the symptoms after four years. As indicated in table 2, other investigators[8] have had less favor-

7. This protein hydrolysate was obtained from the Arlington Chemical Company, Yonkers, N. Y.

8. Blumberg and Cassady.[1] Schwarz, H.; Kohn, J. L. and Weiner, S. B.: Lipid Nephrosis, Am. J. Dis. Child. **65**:355 (March) 1943. Heymann, W., and Startzman, V.: Lipemic Nephrosis, J. Pediat. **28**:117 (Feb.) 1946.

TABLE 2.—*Reported Cases of Nephrosis With Subsequent Measles*

	Case	Duration of Nephrosis Before Onset of Measles	Length of Remission	Relapse
Schwarz, Kohn,* Weiner	1	14 months	6 months	Intermittent periods of albumin in urine
	2	6 months	?	Albumin in urine
Heymann,* Startzman	1	8-16 months	Albumin-free 4 days	Bronchopneumonia
	2		Albumin-free 18 days	Pharyngitis
	3		None	Died of pneumonia
	4		None	Patient's condition unaffected
	5†		None	Patient's condition unaffected
Blumberg, Cassady	1	49 days	10+ months	None to date
	2	6 months	3.5 months	Relapse
Meizlik, Carpenter	1	17 days	10+ months	None despite subsequent infection
	2	4 months	8+ months	None despite subsequent infection
	3	4 months	4 years	None despite subsequent infection

*Personal communication
†Heymann, W.: Personal communication to authors

able results with measles therapy; in the 9 cases tabulated only 1 patient, a patient of Blumberg and Cassady, maintained improvement.

A possible explanation of the more favorable results obtained in our patients may be due to the occurrence of measles in the early stages of the kidney disease. In cases 1 and 2 the virus infection developed during the first attack of nephrosis. In case 3 the nephrosis, although not in the initial stage, was of only four months' duration when the measles rash appeared. As indicated in table 2, the only patient who maintained improvement was the one whose nephrosis was of less than six months' duration when the measles developed.

Another possible contributory factor in 2 of our patients may have been that protein hydrolysate was an adjunct therapeutic measure previous to and following measles. It has been observed by 1 of us (A. M. C.) that when protein hydrolysates, especially of lactalbumin, are administered in the early stages of nephrosis uncomplicated by measles there is a rise in the blood protein level, although this rise is not accompanied by appreciable clinical improvement or loss of edema.

A further interesting observation, as shown in table 1, is that on discontinuance of lactalbumin hydrolysate the total serum protein fell, although the albumin-globulin ratio was not reversed, as it had been before the onset of measles. We believe, therefore, that the use of a hydrolysate, preferably lactalbumin, is desirable after measles because of its tendency to maintain a high blood protein level. The essential component of such a hydrolysate is its nitrogen content. In treatment in the foregoing cases, we have used four products. These preparations differ widely in their nitrogen content. The equivalents in grams of total protein per tablespoonful are: "lactamin," 8; "essenamine," 20; "aminoids," 4; "amiprote," 5. The dosage was calculated at 1.5 Gm. of protein content per pound of body weight, irrespective of the amount of protein obtained in the daily diet. This therapy should be continued until the blood serum levels return to normal and during any period of subsequent infection.

COMMENT

The exact mechanism by which the virus of measles favorably modifies the course of the nephrotic syndrome is still unknown. Fever per se is apparently not the all-important factor because no similar effect is obtained by fever therapy.[9] An explanation of alteration in metabolism is suggested by Blumberg and Cassady[1] and Hutchins and Janeway,[2] who base their conclusion on the fact that a rather rapid change toward normal occurs in the serum proteins after an infection with measles. In

9. Aldrich, C. A.: Nephrosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., vol. 3, chap. 28, p. 31.

the 2 cases on which we have chemical data (table 1) no immediate return of the blood serum proteins to normal levels occurred. The rise that eventually took place we attribute to constant oral medication with hydrolysates. As already noted, the total protein levels fell with the withdrawal of hydrolysates. Although diuresis set in almost immediately after the measles infection, the return to normal of the blood protein level has been much slower and more gradual. This observation apparently would indicate that the initial change wrought by measles toxin occurs in the kidney itself; we are inclined to attribute the change to alteration in the colloidal complex of the glomerular filter.

While we hesitate to say that patients are definitely cured—we are only too well aware of the relapse that has often followed many months of remission—nevertheless, the improvement has been so gratifying that we feel strongly that the induction of measles should be considered as a therapeutic measure in patients showing the nephrotic syndrome. The preliminary report of Hutchins and Janeway[2] on experimentally induced measles in cases of nephrosis would appear to offer a therapeutic approach to this problem.

SUMMARY

In 3 children with nephrosis spectacular and apparently permanent improvement occurred after intercurrent infection with measles.

In all 3 patients the measles occurred in the early stages of the nephrotic syndrome.

Hydrolysate of lactalbumin prescribed during and following measles is a possible beneficial contributory factor.

NOTE.—During the interim of nine months between the submission of the manuscript and the publication of this paper the patients have maintained improvement.

Case Reports

GENERALIZED ARTERIAL CALCIFICATION IN INFANTS

JOHN T. PRIOR, M.D., AND VICTOR W. BERGSTROM, M.D.
BINGHAMTON, N. Y.

ARTERIAL calcification, usually thought of as a disease of adult life, has been noted at birth and in the first few weeks of neonatal life. The literature on this subject has been excellently reviewed by Stryker[1] and more recently by Field.[2] To date, 21 cases have been described. Within the last two years, 2 cases have come to autopsy in this institution. Because of the rareness of the condition and since the pathologic findings are so unique, we feel that the reporting of these cases will be of significant value. The diagnosis was not made in either instance until necropsy.

REPORT OF AUTHORS' CASES

CASE 1.—*History.*—S. S., a 4 week old white girl, was admitted to the hospital on Aug. 4, 1945 with a history of periods of cyanosis, regurgitation after nearly every feeding and a failure to gain weight since birth.

Examination—Physical examination on admission revealed a poorly developed, poorly nourished infant weighing 5 pounds, 10 ounces (2,551.46 Gm.). Respirations were labored and the rate was 26 per minute. Cyanosis of the extremities was present. The pulse rate was 112 per minute and the rectal temperature was 98.4 F. On examination the heart and lungs were not unusual. The tentative diagnosis was pyloric stenosis or spasm. Roentgenograms, including those taken after a barium meal, failed to reveal anything abnormal. The diet was changed to thick feedings—barley gruel or pablum with similac, and 0.002 Gm. of atropine sulfate was given after feeding. Calcium gluconate, 5 Gm. three times a day, was given for the first two weeks, after which it was combined with dicalcium phosphate, 5 Gm. three times a day, and "drisdol" (crystalline vitamin D_2 in propylene glycol) 3 minims (0.18 cc.) daily. These drugs were continued until death on December 16.

The child gained weight slowly and continued to have cyanotic periods which bore no relation to feedings but seemed to be associated with the accumulation of mucus in the throat. Clonic convulsions involving, at times, the entire body or the face, and occasionally limited to one extremity, appeared. These convulsions were precipitated by the sudden awakening or moving of the child.

From the Department of Pathology, Binghamton City Hospital.

1. Stryker, W.: Arterial Calcification in Infants, with special Reference to the Coronary Arteries, Am. J. Path. **22**:1007-1019 (Sept.) 1946.

2. Field, M.: Medical Calcification of Arteries of Infants, Arch. Path. **42**: 607-618 (Dec.) 1946.

Opisthotonos was described. The temperature ranged between 99 and 103 F. with an occasional rise to 105 F. (by rectum). Respirations continued to be labored. At this time (Dec. 2, 1945) diagnosis of a chronic subdural hematoma was considered. Results of laboratory studies were as follows: Repeated urinalyses

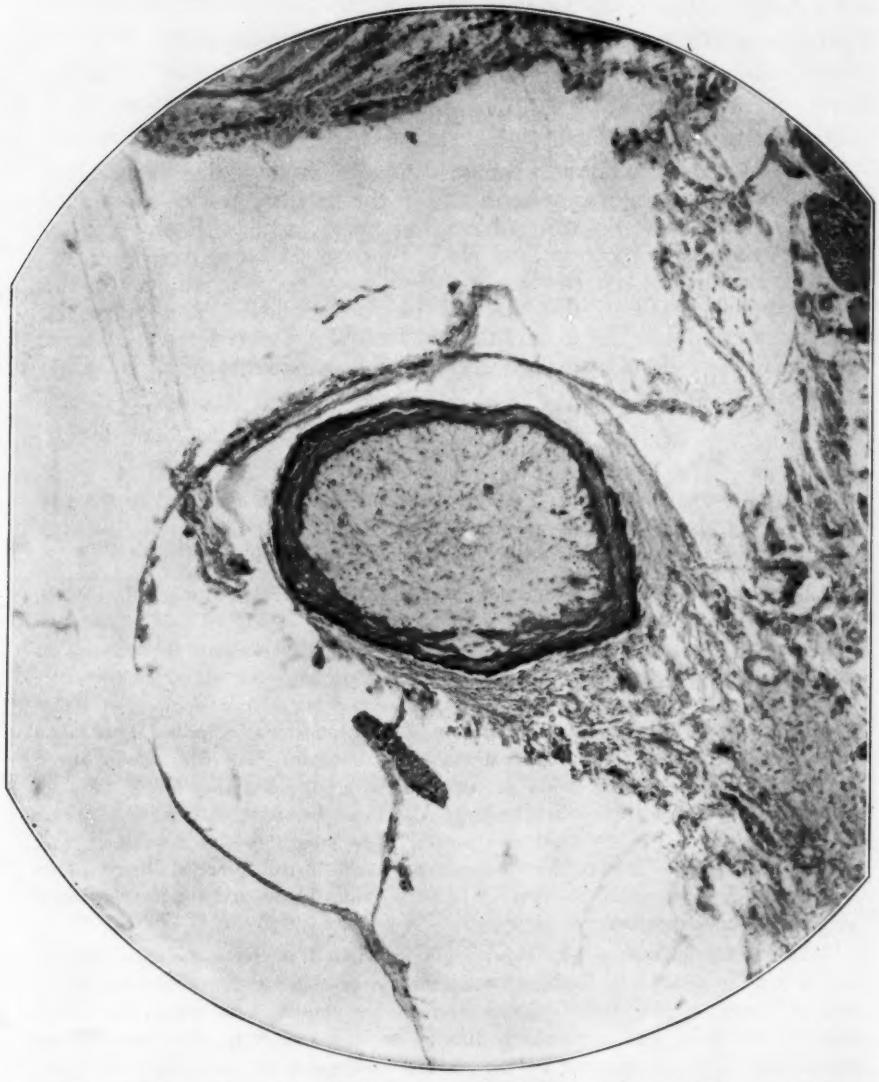

Fig. 1 (case 1).—Calcification along the internal elastic lamina and immediately central to it in a coronary artery. The lumen is nearly completely obliterated by fibroblastic proliferation.

and blood cultures gave normal results. No reaction was obtained in the complement-fixation test for evidence of syphilis. A complete blood count revealed: 2,920,000 red blood cells per cubic millimeter, with 8.5 Gm. of hemoglobin; 13,400 white blood cells per cubic millimeter, with 50 per cent polymorphonuclears

and 50 per cent lymphocytes. Examination of the spinal fluid disclosed 3 lymphocytes and no globulin; culture showed no growth of bacteria. The result of the gum mastic test was 000000. Examination of the sputum failed to demonstrate acid-fast bacilli on direct examination. The blood contained 11.7 mg. of calcium per hundred cubic centimeters, cholesterol 250 mg. and chlorides 760 mg.

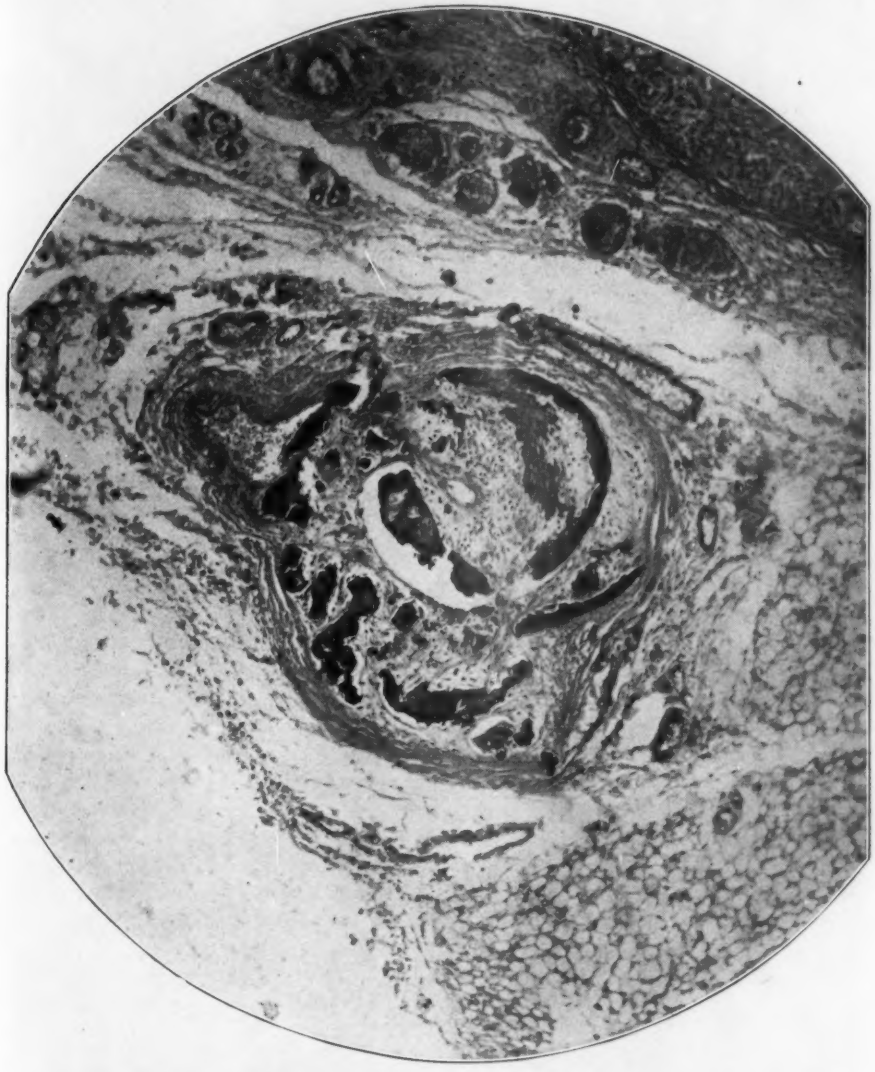

Fig. 2 (case 1).—Fragmentation of calcium due to fibroblastic proliferation in a periadrenal artery. A very small lumen is still identifiable.

Roentgen studies of the chest on December 2 revealed a globular heart with slight enlargement. The lungs and diaphragm did not appear unusual, and no enlargement of the thymus gland was noted. Because of severe dyspnea with cynosis the infant was kept in an oxygen tent continuously the last few hours before death.

Fig. 3 (case 1).—Calcification in the meningeal arteries. All layers of the vessel are involved in one area.

Necropsy (one hour after death).—The body was that of a poorly developed poorly nourished white female infant. The thymus gland was not enlarged. Both pleural cavities contained a small amount of serous fluid. Marked sclerosis was noted throughout the course of the coronary arteries, which were tortuous and had a "pipe-stem" consistence. Nothing unusual was noted in the valves and chambers and no congenital abnormalities were present. Although somewhat flabby, the myocardium was not otherwise remarkable. Section of the lungs disclosed a slight reddening of the bronchial mucosa and diffuse areas of consolidation throughout. The cut surfaces of the kidneys were pale, with distinct markings. Examination of the remaining organs, including the brain, showed no significant gross pathologic changes.

Microscopic Examination.—The process noted in the coronary arteries in this case was repeated in other vessels of the same caliber elsewhere in the body and is identical with the changes seen in the second case to be described. Calcium was deposited both as a complete ring and at intervals along the internal elastic lamina with extension peripherally and centrally to it. This membrane, however, could still be identified as a bright acidophilic line. There was intimal fibroblastic proliferation resulting in marked narrowing or obliteration of the vessel lumens (fig. 1). Recanalization occurred in some instances. Fibrosis and lymphocytic infiltration were present in the media of the vessels. The adventitial layer contained patchy areas of calcification. There was some fibrous tissue replacement of the myocardial fibers, and occasionally calcium plaques without relation to vessels were seen. The individual muscle fibers were swollen, and there was marked variation in the size of their nuclei. Slight calcium deposits were seen in the papillary muscles. In the lungs the alveolar spaces were filled with red blood cells, serum and macrophages containing hemosiderin. The pulmonary arteries had unusual nodular medial thickenings which projected deep into the vessel lumens. Slight congestion of the liver was noted. Examination of the splenic, uterine and periadrenal arteries revealed changes similar to those described in the coronary vessels (fig. 2). One change not seen in any of the other tissues examined was found in the adrenal cortex. Here, dense masses of calcium, apparently deposited at the sites of small capillaries, were fused to form sheets, resulting in the destruction of adrenal parenchyma. Some fine deposits of calcium were seen in these parenchymal cells. Examination of the kidneys disclosed only great dilatation of some convoluted tubules. In the large meningeal arteries of the brain were changes similar to those described for the coronary arteries, but the calcification had extended in some instances to involve all three layers of the vessels (fig. 3). Some capillaries in the parenchyma of the brain were completely calcified, while many others showed large or small plaques projecting as excrescences either centrally into the lumens or peripherally into the perivascular spaces.

In the light of the autopsy observations, the roentgenograms were reexamined and calcification could be readily recognized in the vessels of the upper arms and thighs.

Case 2.—*History.*—A 3 month old white girl, was admitted to the hospital on Feb. 26, 1946 with a history of sudden onset of marked dyspnea and listlessness occurring six hours previous to admission. The mother had mild toxemia during pregnancy, but this child was delivered at term apparently normal.

Examination.—Physical examination on admission revealed a fairly well developed, well nourished infant with an ashen gray color. Extreme apathy was exhibited, and the child moved only when disturbed. The heart rate was slow,

and there were no cardiac murmurs; otherwise the physical findings were not remarkable. Oxygen and respiratory stimulants were given, but the infant died one hour after admission.

Necropsy (one hour after death).—No enlargement of the thymus gland was noted. The heart appeared somewhat smaller than normal, and several small subepicardial hemorrhages were noted over the left base posteriorly. Moderate dilatation of the left ventricle was present and the papillary muscles of both ventricles appeared fibrous in consistence. Both coronary arteries showed definite thickening, with diffuse deposition of calcium (fig. 4). No definite occlusion of the lumens could be found. An area measuring 1 cm. in diameter noted on the posterior wall of the left ventricle was redder than the rest of the heart. The lungs revealed only patchy congestion at their peripheries. The splenic and renal

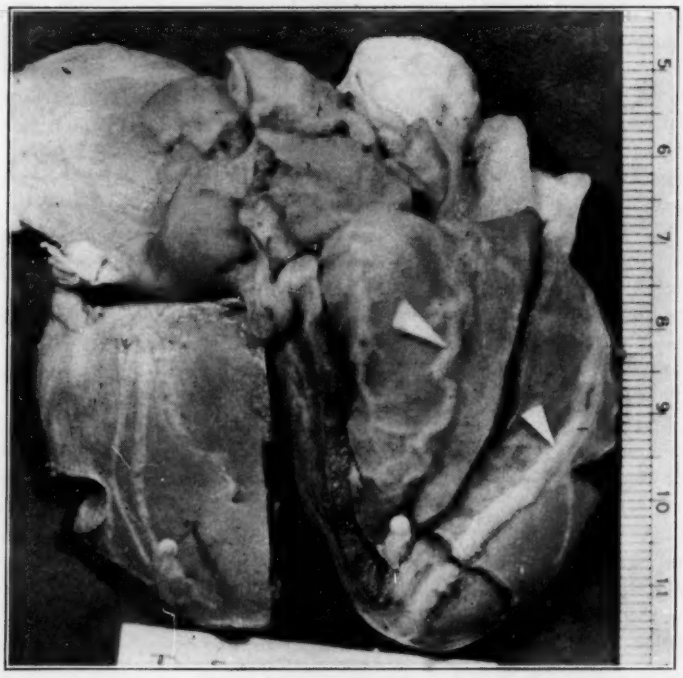

Fig. 4 (case 2).—Heart demonstrating tortuous and "pipe-stem" coronary arteries.

arteries showed thickening and calcification, grossly resembling that described in the coronary arteries. No changes were noted in the thyroid and parathyroid glands and the remaining organs were not remarkable. A specimen of blood taken at this time was found to have 9.4 mg. of calcium per hundred cubic centimeters and a serum alkaline phosphatase level of 6.2 units.

Microscopic Examination.—The coronary arteries were the sites of calcification along the internal elastic lamina and great intimal fibroblastic proliferation with some calcium deposition in this new growth. A subacute infarction was seen in the myocardium, where the muscle fibers were decidedly swollen and degenerated, with pyknotic nuclei present, and there was a diffuse increase in fibrous tissue. These degenerative changes were also noted in the

papillary muscles. The alveolar spaces of the lungs were filled with serum, red blood cells and hemosiderin-laden macrophages. Congestion of the liver and splenic sinusoids was present, and the splenic artery was markedly calcified (fig. 5). This calcific and fibroblastic process was best exemplified in the pancreatic arteries (figs. 6 and 7). The large arteries in the periadrenal tissues

Fig. 5 (case 2).—Splenic artery showing extensive calcification in all three layers.

showed changes similar to those just described, but in addition, giant cells, representing a reaction to calcium, were noted at the intima-medial junction. Calcification and fibroblastic proliferation were present in the uterine arteries. In the aorta there were intimal proliferation and deposition of calcium in the

outermost zone of the media while the internal elastic lamina was uninvolved. These deposits of calcium seemed to be related to elastic fibers. There was some deposition of calcium in the renal convoluted tubules, and the renal arteries showed calcification and fibroblastic proliferation of the intimas. The bone marrow showed no changes in the sections examined.

COMMENT

Twenty-one cases of arteriosclerosis occurring in infants have been reported in the literature. The histologic picture described in the blood

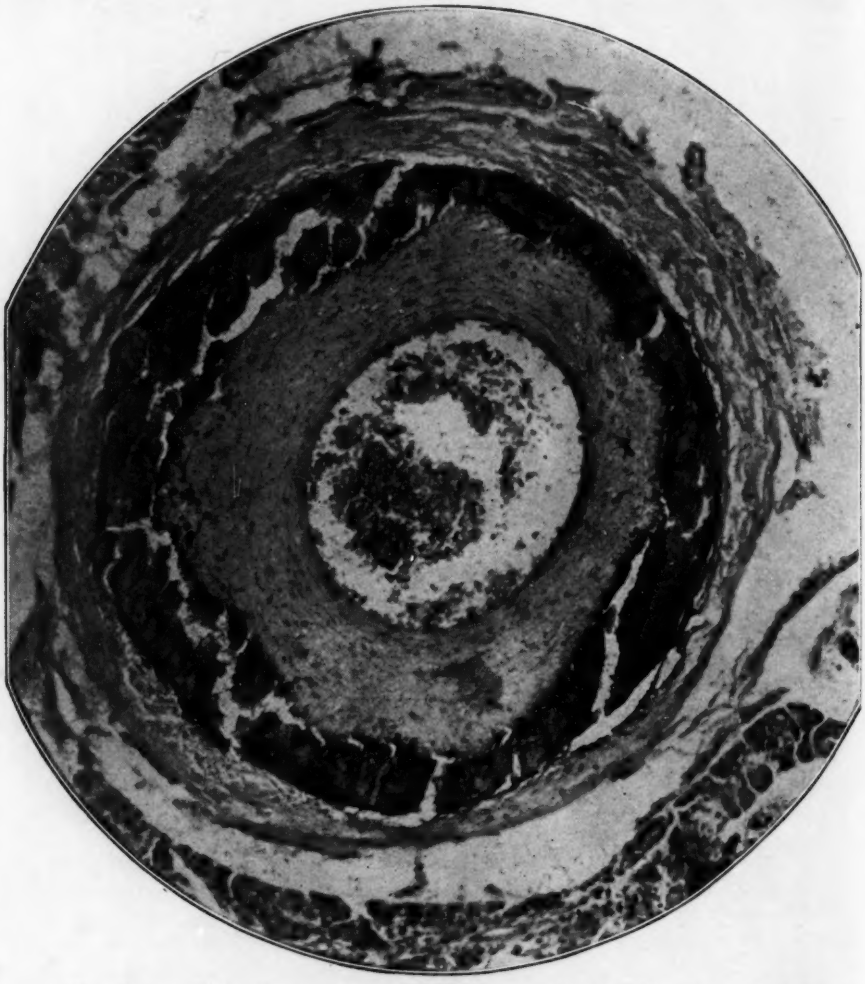

Fig. 6 (case 2).—Pancreatic artery demonstrating calcification and intimal fibroblastic proliferation.

vessels of all of them shows calcification in the internal elastic lamina as well as immediately central and peripheral to it. Intimal fibroblastic proliferation appears to be an associated lesion resulting in definite or complete obliteration of the lumen. In some instances there is subse-

quent recanalization. In the cases reported this process appears to affect only vessels of about the caliber of the coronary arteries, but in our cases even large arteries, including the aorta, were involved. There was apparently no predilection for any organ.

The cause of this condition has never been satisfactorily explained. Among the theories postulated, seven are described most frequently:

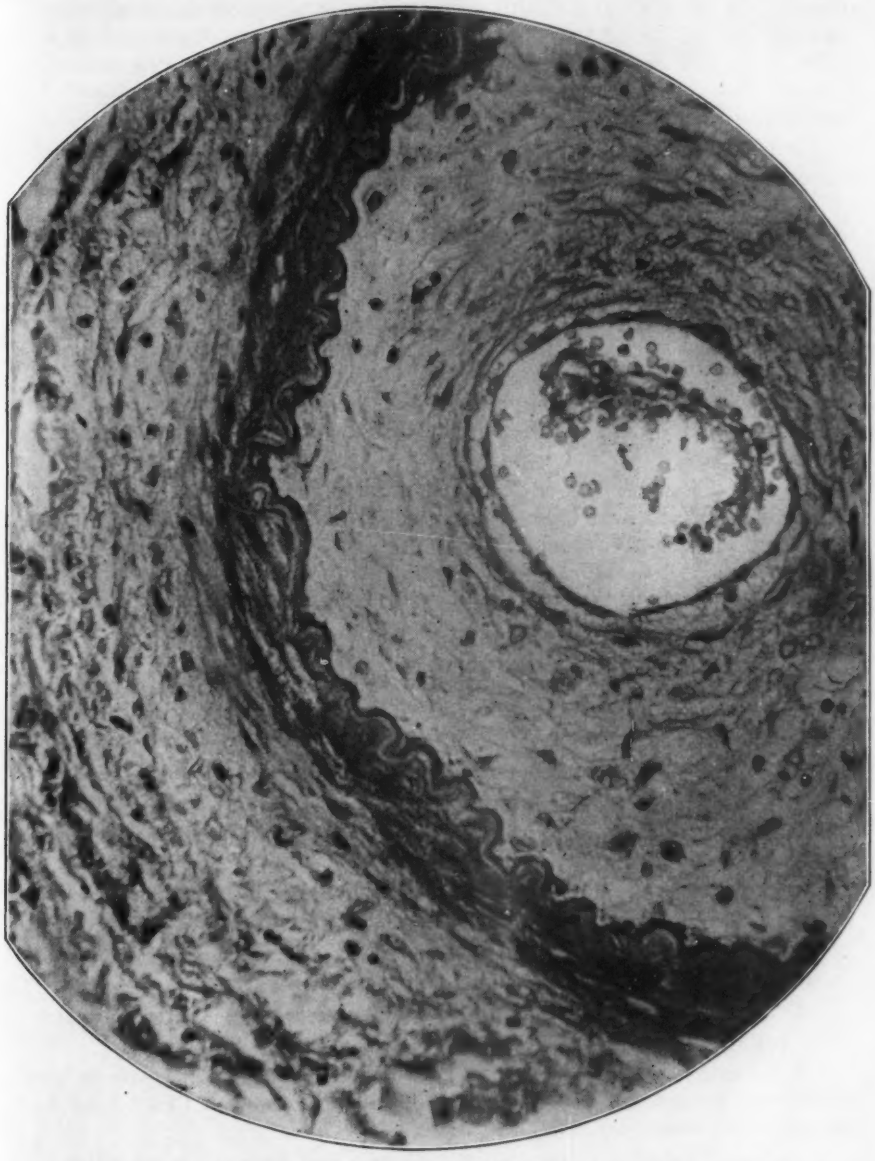

Fig. 7 (case 2).—High power magnification of a pancreatic artery showing a prominent internal elastic lamina with calcification peripheral to it.

1. Infections: In the cases reported by Surbek,[3] Forrer,[4] and Lightwood[5] accompanying infections were reported. In our second case the mother had mild toxemia of pregnancy. A complement-fixation test for evidence of syphilis is reported only in our first case, in which no reaction was obtained with the infant's blood.

2. Disturbances in the serum calcium and phosphorus: In the cases reported by Lightwood[5] and by Andersen and Schlesinger[6] abnormal calcium and phosphorus values were recorded. Case 1 reported here showed a high normal calcium with markedly elevated cholesterol and chlorides, this infant having received both calcium gluconate and dicalcium phosphate in its diet. Case 2 revealed normal serum calcium and alkaline phosphatase values, this child having received neither vitamin D nor calcium in its diet.

3. Hypervitaminosis D: The cases reported by Andersen and Schlesinger[6] are the only examples in the literature reviewed in which an overdose of vitamin D can be definitely incriminated. Goormaghtigh and Handovsky[7] have demonstrated experimentally in dogs that the process resulting from hypervitaminosis D gives a distinctly different pathologic picture from the lesions described here.

4. Parathyroid lesions: Lesions in these glands would produce their effects through altered serum calcium and phosphorus levels. The parathyroid glands were examined in only 1 case, that reported by Iff,[8] in which he found nothing abnormal. Although the parathyroid glands were examined grossly in one of our cases, we failed to examine them microscopically.

5. Renal lesions: Extensive renal changes were present in the cases reported by Bryant and White,[9] Lightwood,[5] and Andersen and Schlesinger.[6] Milder lesions were present in the cases of Surbek,[3] Forrer,[4] and van Creveld.[10] Calcium deposits were noted in the convoluted tubules in one of our cases, but we feel this to be a result of the process and not an etiologic factor.

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3. Surbek, K.: Ueber einem Fall von kongenitaler Verkalkung, mit vorwiegender Beteiligung der Arterien, Zentralbl. f. allg. Path. u. path. Anat. **28**:25-39, 1917.

4. Forrer, H.: Ausgedehnte Gefassverkalkung im frühen Kindesalter, Inaug. Dissert., Zurich, J. H. Meier, 1930.

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10. van Creveld, S.: Coronary Calcification and Thrombosis in an Infant, Ann. paediat. **157**:84-92, 1941.

6. Allergy: In the 2 cases reported by van Creveld,[10] he states that the mother was asthmatic in one instance, and that there was a family history of asthma in the other.

7. Diseases of bone: Bony changes have been reported in only 1 case, that of Lightwood,[5] in which there was an associated parathyroid hyperplasia.

We believe that the symptoms dyspnea, cyanosis and convulsions in the newborn accompanying roentgen evidence of calcification of vessels should lead one to consider arterial disease and/or myocardial infarction in the differential diagnosis, which must include congenital heart disease and mediastinal tumors.

SUMMARY

Two cases of generalized arterial calcification in infants have been reported. The changes seen in the vessels of these infants, i.e., calcium deposition in relation to the internal elastic lamina with an associated intimal fibroblastic proliferation, are identical with those described in previously reported cases, but larger vessels, including the aorta, were involved. The symptoms occurring in this condition along with roentgen evidence, while not diagnostic, should suggest its possibility.

TUMORS OF THE THYMUS IN CHILDREN

ALFRED E. NEALE, M.D.
AND
MAUD L. MENTEN, M.D.
PITTSBURGH

DESPITE the frequency of hyperplasia of the thymus in early life, tumors of this organ are rare during the first decade. Less than 50 authentic cases have been reported in the last century. During the past year, 2 children with thymic tumors have been studied in the Children's Hospital of Pittsburgh. The first of these growths was malignant and caused death in an 8 year old white girl, and the second was of the benign type and occurred in a 10 year old white boy, who is still living. These 2 tumors are described in this report.

The first thymic tumor found referred to in the literature was a lymphosarcoma in a 19 year old woman described by Cooper in 1832.[1] However, the first case arising in childhood was a lymphosarcoma in a child of 8 years recorded by Grutzner in 1869.[2] In 1873 Gamgee[3] likewise described a lymphosarcoma of the thymus which occurred in a 5 year old girl. In 1911 Rubaschow[4] tabulated 69 previously published cases of malignant conditions of the thymus and critically analyzed them. This author was of the opinion that in several of the earlier cases the data were insufficient to warrant a diagnosis of thymic tumor. Of the reported 24 new growths of the thymus occurring in children, he believed 9 to be of doubtful origin. In 1932 Crosby[5] collected from the literature 166 proved cases of malignant thymic neoplasm. Of this total, 122 were sarcomas and 44 carcinomas. The author listed 20 cases occurring in the age group up to and including 15 years, which period is generally regarded in hospitals as constituting childhood.

Rogatz[6] in a review up to 1939 assembled 8 additional reports of lymphosarcomas[7] and also included a pleomorphic lymphosarcoma occur-

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From the Department of Pathology, University of Pittsburgh, and the Children's Hospital of Pittsburgh.

1. Cooper, A. C.: Anatomy of the Thymus Gland, London, Longman [and others], 1832, p. 3.

2. Grutzner, P.: Ein Fall von Mediastinaltumor durch ein Lymphosarcom bedingt, Berlin, G. Lange, 1869, p. 36.

3. Gamgee, A.: Lymphosarcoma or Lymphadenoma, Edinburgh M. J. **18**: 797, 1873.

4. Rubaschow, S.: Eine bösartige Thymusgeschwulst, Vichows Arch. f. path. Anat. **206**:141, 1911.

5. Crosby, E. H.: Malignant Tumors of the Thymus Gland, Am. J. Cancer **16**:461, 1932.

6. Rogatz, J. L.: Pleomorphous Cell Lymphosarcoma of the Thymus: A Case in an Infant of Two and One-Half Months, J. Pediat. **14**:618, 1939.

ring in a 2½ month old girl, who is the youngest patient with such a growth on record.

Since Rogatz' paper, 4 additional cases[8] of malignant thymic tumors in children have been published and these together with the 1 we are reporting bring the total to 47, with a distribution of 44 cases of lymphosarcoma and 2 of carcinoma.[9] The remaining case, described by Wollstein and McLean[10] was a case of Hodgkin's disease which apparently was primary in the thymus.

In recent years there has been considerable discussion concerning the relation of thymic tumors to myasthenia gravis, but as far as we could ascertain there has been no report of the association of tumor of the thymus with this condition in children.

True benign thymomas are even rarer than the malignant type. All authors agree that the nonmalignant new growths reproduce the normal histologic picture including Hassall's corpuscles, but they differ as to whether or not metastases are an essential feature. Andrus and Foot[11] have cited 5 examples of benign thymoma with metastases in adults and an additional case has been recorded by Sloan.[12] In children, 2 cases without metastases have been reported, 1 by Andrus and Foot[11] and the other by Wyllie and Burrows.[13] We here include an additional case.

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7. Symmers, D.: Malignant Tumors and Tumor-Like Growths of the Thymic Region, Ann. Surg. **95**:544, 1932. Grenet, H.; Isaac-Georges, P.; Louvet, and Arondel: Volumineux lymphosarcome du mediastin avec metastases multiples chez un enfant de 7 ans, Rev. franc. de pediat. **9**:656, 1933. Davidson, M.: A Practical Manual of Diseases of the Chest, London, Oxford University Press, 1935, p. 1493. Wiglesworth, F. W.; Childe, A. E., and Goldbloom, A.: Mediastinal Lymphosarcoma in Childhood, J. Pediat. **9**:331, 1936. Prosser Evans, R. G.: Malignant Tumor of the Thymus Gland, Brit. M. J. **1**:775, 1938.

8. (*a*) Wade, J. L., and Matthews, A. R. K.: Thymic Malignancy, West Virginia M. J. **37**:107, 1941. (*b*) Silva Nunes: Sobre um caso de timoma, Arq. de pat. **10**:336, 1938. (*c*) Bomze, E. J., and Kirshbaum, J. D.: Lymphosarcoma of the Mediastinum, J. Lab. & Clin. Med. **24**:928, 1939. (*d*) Wasserman, P., and Epstein, J. W.: Congenital Carcinoma of the Thymus with Extensive Generalized Metastases, J. Pediat. **14**:798, 1939.

9. Wasserman and Epstein.[8d] Bedford, G.: A Case of Carcinoma of the Thymus with Extensive Metastases in a New-Born Child, Canad. M. A. J. **23**:197 (Dec.) 1930.

10. Wollstein, M., and McLean, S.: Hodgkin's Disease, Primary in the Thymus Gland: Report of a Case in an Infant, Am. J. Dis. Child **32**:889 (Dec.) 1926.

11. Andrus, W. D. W., and Foot, N. C.: Report of a Large Thymic Tumor Successfully Removed by Operation, J. Thoracic Surg. **6**:648, 1937.

12. Sloan, H. E., Jr.: The Thymus in Myasthenia Gravis, with Observations on the Normal Anatomy and Histology of the Thymus, Surgery **13**:154, 1943.

13. Wyllie, W. G.: Myasthenia Gravis (Two Cases), Proc. Roy. Soc. Med. **39**:591, 1946.

REPORT OF CASES

Case 1 (benign thymoma).—E. S., a 10 year old white boy, was first admitted to the Children's Hospital of Pittsburgh on Jan. 28, 1946, with a chief complaint of fever, cough, shortness of breath, nausea and vomiting. The tentative diagnosis was pulmonary tumor. Physical examination revealed diminished breath sounds and dulness to percussion over the right side of the chest. In roentgenograms of the chest, the middle and lower lobes of the right lung appeared

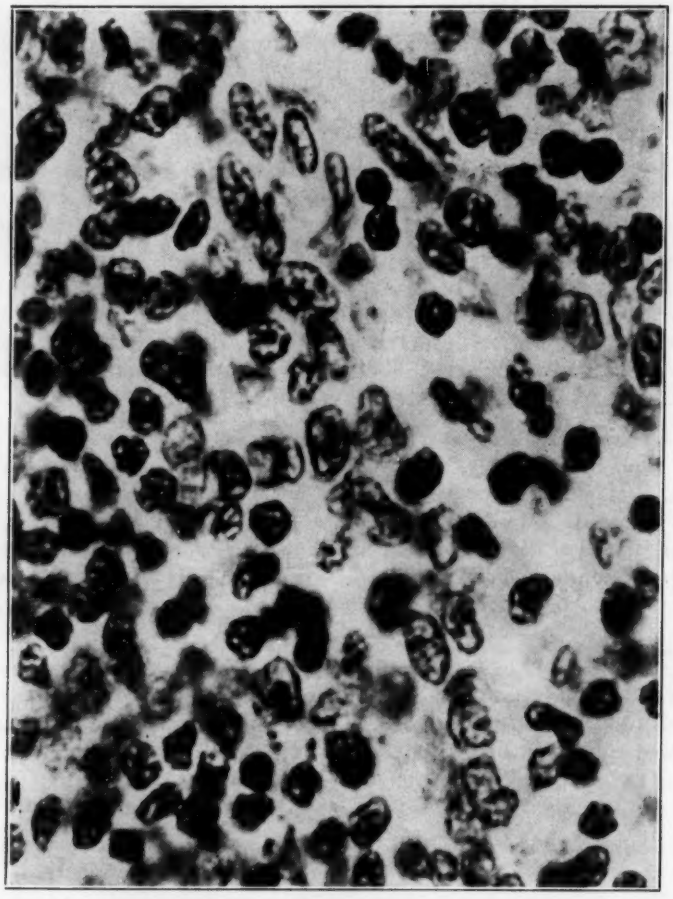

Fig. 1.—Photomicrograph of tumor showing meshwork of reticular cells and epithelial cells distributed singly, in cords or in Hassall's corpuscles.

opaque. On bronchoscopy the impression was pneumonia of the right lower lobe. With penicillin therapy the temperature became normal but the roentgen picture did not change. The patient was discharged on Feb. 12, 1946 with a diagnosis of atelectasis and chronic bronchitis. At home the cough did not improve although he gained 10 pounds (4.5 Kg.), and he was readmitted on March 10, 1946. On physical examination at that time the patient had bulging of the right anterior wall of the chest with widening of the interspaces and some deviation of the trachea to the right. On bronchoscopy, a possible tumor of the lung with medi-

astinal involvement was diagnosed. All laboratory tests gave normal results. On March 25, 1946 an exploratory operation of the right side of the chest was performed by Dr. E. W. Meredith and a large tumor was found in the mediastinum. The overlying flap of reflected pleura was opened, to expose a lobulated friable mass. A small portion of the growth was removed for diagnosis, but after exploring the field complete removal was deemed impossible because the mass extended down to the diaphragm, up into the neck, posteriorly around the great vessels and laterally to the hili of the lungs. No metastases were present.

Microscopically, the tumor was composed of islands of thymic tissue embedded in an adipose stroma, but without a definite capsule. In all areas the component parts of the thymus were present, but the architectural pattern differed. Three distinct pictures were seen, depending on the disposition of the small lymphocytes on the background of epithelial cells and reticulum. First, the gland appeared as normal thymus with a distinctly demarcated cortex and medulla. The cortex was made up of a stroma of scattered reticular cells infiltrated with small closely packed lymphocytes arranged in peripheral scallops, and the medulla was composed of a fairly compact meshwork of the reticular cells with epithelial cells distributed throughout singly, in cords (fig. 1) or in Hassall's corpuscles. A few scattered lymphocytes and eosinophils were also present. Second, the cortex and medulla were uniformly infiltrated with lymphocytes and Hassall's corpuscles were present in both, but smaller in size in the cortex. The reticular pattern of the medulla was obscured. Third, in some areas there was a complete reversal of situs of cortex and medulla, with dense collections of lymphocytes in central areas and a loose reticulum with a few lymphocytes in the peripheral scallops. A diagnosis of nonmalignant thymoma was made on the basis of the foregoing findings.

Because of the inoperability of the tumor, the patient was treated with high voltage roentgen therapy. Between April 10 and June 29, 1946 he received a total of 7,850 roentgens to the chest applied through a ¾ inch (1.91 cm.) copper filter at 200 kilovolts, without obvious regression of the mass. This amount is many times that used to cause regression in thymic hyperplasia. The patient has improved clinically, gained weight and become symptomless, but at the present time the mass has not materially regressed.

Case 2 (lymphosarcoma).—M. K., an 8 year old white girl, was first admitted to the Children's Hospital of Pittsburgh on March 2, 1946 with a chief complaint of fever, headache and pain in the chest. Pneumonia was suspected and confirmed by roentgenograms, which also revealed a round mass in the mediastinum. The former resolved with penicillin therapy, but the mass persisted. The child was discharged from the hospital on March 7, 1946.

On the next two admissions (March 21 and April 3, 1946) she complained of increasing dyspnea, pain in the chest, orthopnea and swelling of the face and neck. Physical examination revealed a child in acute respiratory distress with a mild cyanosis of the lips and ear lobes. No lymph nodes were palpable. There was marked tortuosity of the superficial veins of the anterior wall of the chest, and the chest was flat to percussion from the fourth rib to the diaphragm anteriorly and posteriorly. The wall of the chest was pushed markedly to the left, so that the apex of the heart was situated in the left axilla. The heart sounds were of good quality. The abdomen was distended but without tenderness or palpable masses. Thoracenteses done on 10 different occasions gave a total of 6,450 cc. of bacteria-free serosanguineous fluid containing a few neutrophils. The patient required oxygen during, and "coramine" (nikethamide) after, each tap. On April 30, 1946, one hour after the last thoracentesis, the patient died. Red, white and differential blood counts and results of urinalyses were within normal limits. The nonprotein nitrogen was not elevated, and the blood proteins were normal.

At autopsy, performed one hour after death, the tumor mass almost filled the thoracic cavity and was attached to the thoracic wall by fibrous adhesions. The bulk of the tumor was on the right side of the chest but a large part also extended far into the left side, as well as from the diaphragm below to the suprasternal notch above. It encircled the great vessels of the neck. On removal the tumor, measuring 22 x 20 x 16 cm., was well encapsulated, white and firm. The right lung was adherent to the thoracic wall and firmly attached posteriorly to the tumor mass. The lung parenchyma was reduced in size and was firm in consistency. Throughout both lungs were many small metastatic shotty nodules.

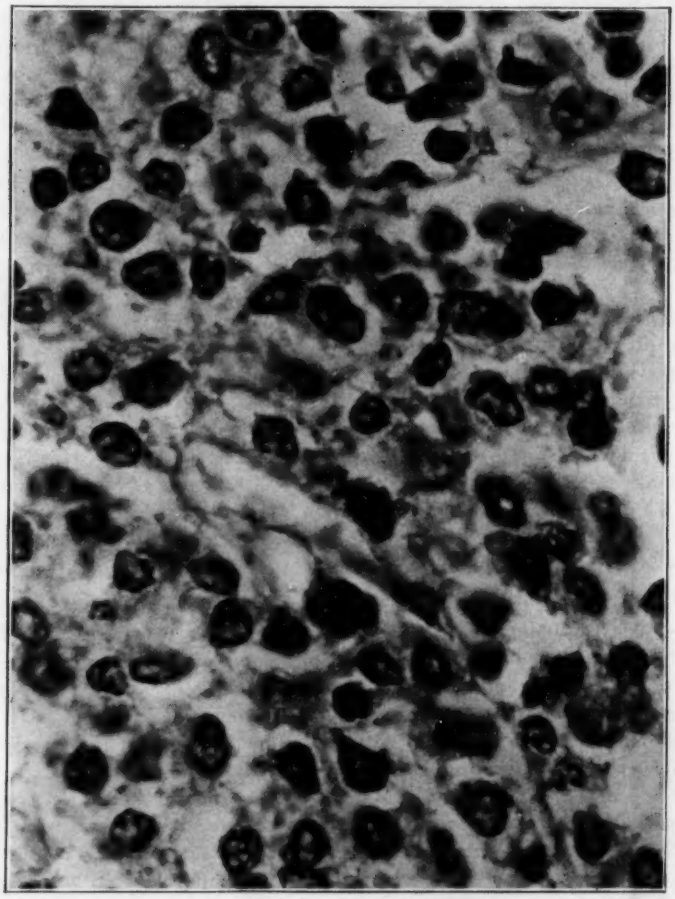

Fig. 2.—Photomicrograph of tumor in case 2, showing large cuboidal cells.

The heart was embedded in the lower portion of the tumor mass. The pericardial surface was roughened and yellow-green. Many tumor nodules were present in the auriculoventricular groove. The musculature and valves of the heart appeared normal. The great vessels and trachea coursed through the center of the mass and were compressed by it.

One small tumor nodule was present in the surface of the left lobe of the liver. This organ showed the characteristic mottling of chronic passive congestion.

No metastases were found in the gastrointestinal tract or spleen. Several large tumor nodules were seen invading the interlobular septums of the pancreas.

The surface of each kidney was studded with metastatic growths. On section these extended through the cortex into the medulla. The architecture of both adrenals was distorted by small tumor masses.

The anatomic diagnoses were mediastinal tumor with infiltration of the pericardium and lungs; metastases to liver, lungs, pancreas, adrenals and kidneys; pressure atelectasis of lungs; bilateral bronchopneumonia; chronic passive congestion of liver and spleen; fibrous adhesions of pleura and pericardium, and ascites.

Microscopically, the tumor was composed of small lobules of cells, separated by bands of connective tissue. The tissue had a loose texture with a moderate number of thin-walled capillaries and scattered areas of necrosis. With a reticulum stain, the reticulum fibers, four to seven in number, formed a thin encircling band around the vessels at the periphery of the lobules. From these main fibers, fine branching fibrils extended for a short distance into the lobules. In the older parts of the section the reticulum was more widespread, but in the main the epithelial cells were free of reticulum fibers. The cells, although somewhat pleomorphic, were large and cuboidal with a deeply staining vesicular nucleus and a faintly granular basophilic cytoplasm (fig. 2). A few multinucleated cells and mitotic figures were found. A sparse infiltration of small lymphocytes was noted in some places. No distinct Hassall's corpuscles were seen but occasionally what was thought to be a cluster of epithelial cells was noted, and sometimes these resembled the fragmented portions of Hassall's bodies. The cellular structure of the primary tumor was maintained in the metastases, the presence of which in liver, pancreas, kidneys and adrenal glands frequently caused a pressure atrophy and distortion of the organ architecture.

COMMENT

Thymic tumors, although rare, present several points of interest. In children the majority of mediastinal masses arise in the thymus, and rarely tuberculosis, substernal thyroid, infections and tumor developing in the lymph nodes of this region may confuse the diagnosis. Of the masses of thymic origin, the greatest number are hyperplasias and can be differentiated from the occasional thymic neoplasm by their prompt regression under roentgen therapy. The tumors, because of their intimate association with the great vessels and the trachea, are more prone to cause compression symptoms, such as dyspnea and cyanosis. An early diagnosis is imperative because most of the malignant, in contrast to the benign, "thymomas" respond favorably to roentgen irradiation. The benign growths, if not too extensive, can be removed surgically. Whether the presence of metastases to nearby organs places the thymomas in the benigh or malignant category is apparently a moot question. Andrus and Foot[11] include in the benign group, designated "noncancerous" in Foot's textbook,[14] those which do and those which do not metastasize. A possibility exists that related growths in neighboring

14. Foot, N. C.: Pathology in Surgery, Philadelphia, J. B. Lippincott Company, 1945, p. 310.

organs are not true metastases but heterotopic foci which have coincidentally responded to the same stimuli as the main thymus. Examples of such aberrant growths have been described by Heller[15] and others.[16] In many animals the anlage of the thymus varies considerably. In man branchial pouch III is a constant embryologic source,[17] and in 42 per cent of the cases branchial pouch IV also contributes to the formation of the organ according to Van Dyke.[18] This variable anlage may influence the final distribution of the thymus.

Reversal of situs of cortex and medulla is not unique for benign thymoma, as we have occasionally observed this alteration in position of these two components in thymuses removed routinely at autopsy.

Whether the presence of reticulum fibers contributes essentially to the classification of malignant thymomas seems problematic. The claim that these fibers develop from epithelium as well as reticuloendothelial cells and connective tissue would seem to be nullified by the findings of Norris[17b] and Smith and Ireland[19] that thymic reticular fibers are derived primarily from the vascular walls and these primary strands, enveloping the blood vessels, send fine radiating fibrils among the surrounding thymic cells. The relatively poor vascular supply of the thymic cortex coexistent with its minimum of reticulum fibers would tend to corroborate this finding.

SUMMARY

This report of 2 cases of tumor arising in the thymus emphasizes the rarity of thymic neoplasms in children.

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16. Sharp, E. W.: A Case of Persistent Aberrant Thymus, Lancet **1**:436, 1906. Gilmour, J. R.: Some Developmental Abnormalities of the Thymus and Parathyroids, J. Path. & Bact. **52**:213, 1941. Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1918, p. 536.

17. (*a*) Cooper, E. R. A.: The Thymus Gland, in the Histology of the More Important Human Endocrine Organs at Various Ages, Edinburgh, Oxford University Press, 1925, p. 20. (*b*) Norris, E. H.: The Morphogenesis and Histogenesis of the Thymus Gland in Man: In Which the Origin of the Hassall's Corpuscles of the Human Thymus Is Discovered, Contrib. Embryol. **27**:191, 1938.

18. Van Dyke, J. H.: On the Origin of Accessory Thymus Tissue, Thymus IV: The Occurrence in Man, Anat. Rec. **79**:179, 1941.

19. Smith, C., and Ireland, L. M.: Studies on the Thymus of the Mammal: Distribution of Argyrophil Fibers from Birth Through Old Age in Thymus of Mouse, Anat. Rec. **79**:133, 1941.

AGENESIS OF CORPUS CALLOSUM IN INFANCY: CLINICAL AND ROENTGENOLOGIC ASPECTS

ELIAS SAVITSKY, M.D.
AND
VINCENT A. SPINELLI, M.D.
NEW YORK

CONGENITAL ABSENCE of the corpus callosum and the anomalies that occur in association with this condition have been the subjects of many studies since the first description of this entity by Reil[1] in 1812. In 1922 Mingazzini[2] collected 71 cases in his classic monograph on the corpus callosum. Baker and Graves[3] in 1933 collected an additional 11 cases. To date, well over 100 cases have been reported. Until 1934 it was uniformly recorded as an incidental observation at necropsy. Davidoff and Dyke[4] and Penfield and Hyndman[5] were the first to establish the criteria for the pneumoencephalographic diagnosis of agenesis of the corpus callosum. Twenty-two cases have been diagnosed by roentgenologic means, 10 of which were confirmed by necropsy studies or at operation. More adequate opportunities were thus afforded for accurate study of the clinical aspects of these cases and for better classification of some of the instances of mental deficiency and neurologic disorder of obscure origin that come to the attention of the pediatrician and the neurologist.

The case to be reported is the eleventh in which premortem diagnosis and necropsy studies have been correlated. This patient and that reported on by Reeves[6] are the youngest patients for whom the diagnosis of agenesis of the corpus callosum were made by air studies.

From the Neuropsychiatric and Pediatric Services, Morrisania City Hospital.

1. Reil, cited by Bunts and Chaffee.[8]

2. Mingazzini, G.: Der Balken, Eine anatomische, physiopathologische und klinische Studie, Berlin, Julius Springer, 1922.

3. Baker, R. C., and Graves, G. O.: Partial Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. **29**:1054 (May) 1933.

4. Davidoff, L., and Dyke, C. G.: Agenesis of the Corpus Callosum: Its Diagnosis by Encephalography, Am. J. Roentgenol. **32**:1, 1934.

5. Penfield, W., and Hyndman, O.: Agenesis of Corpus Callosum, Tr. Am. Neurol. A. **60**:182, 1934.

6. Reeves, D. L.: Congenital Defects of the Cranial Nerves, Bull. Los Angeles Neurol. Soc. **4**:184, 1939.

REPORT OF CASE

P. P., a white girl 6 months of age, was admitted to Morrisania City Hospital Nov. 20, 1946 because of several attacks of generalized convulsions and because of abnormal enlargement of the head since birth. The patient was the youngest of 3 children. The family history revealed no nervous or mental disease. The 2 siblings were perfectly normal. Pregnancy and delivery were within normal

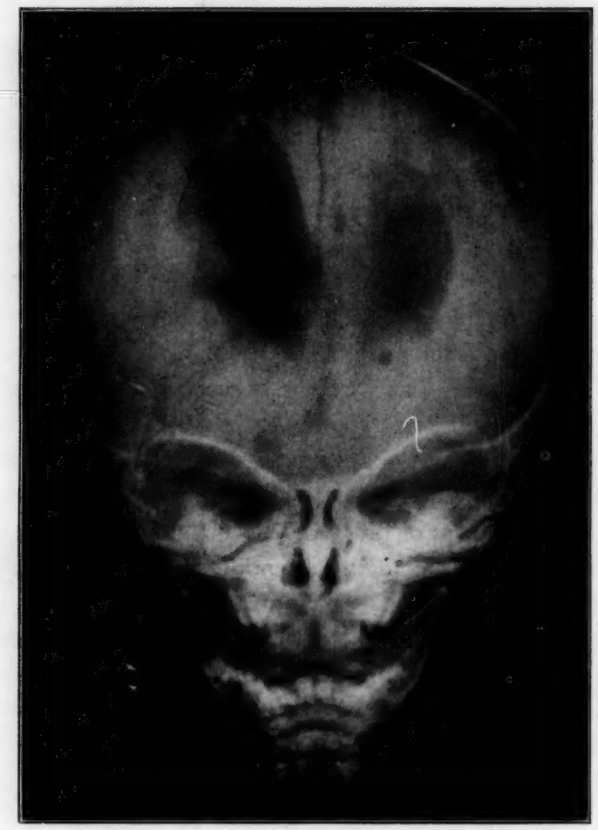

Fig. 1.—Anteroposterior ventriculogram of infant P. P. showing agenesis of corpus callosum.

limits. From the birth the mother had noticed that the child's head increased in size at a rate greater than normal. Mental and motor development were decidedly retarded. The child lay on its back all the time. Spontaneous motor movement and response to stimuli were slight. She failed to hold up her head. The first convulsion was noted on the fifteenth day after birth. In the next six months two more convulsions occurred. All seizures were generalized in character and lasted about fifteen minutes each.

On her admission to the hospital the child appeared of normal development and well nourished. The head was abnormally large, and the anterior fontanel was wider than normal, with definite bulging and pulsation. The child lay

quietly in bed. There was no focal weakness of the extremities. The pupils were equal and regular and reacted to light. Ophthalmoscopic examination revealed abnormal pallor of optic disks. The eyes appeared to deviate downward. Response to auditory and visual stimuli was slight. Follow movements of the eyes were elicited. The results of the objective examination were otherwise normal. A spinal tap showed fluid under pressure of 350 mm. of water; the fluid was clear with no cells, and chemical and cultural studies revealed no abnormality.

Course.—Subdural tap was performed, and the right lateral ventricle was entered accidentally. A ventriculogram was obtained (fig. 1), and the report was as follows: "There is an irregular dilatation of both lateral ventricles, especially in their posterior portion. A moderate amount of fluid is present in each ventricle. The ventricles are also slightly separted. The third ventricle is incompletely filled. A small amount of air is present in the subarachnoid space anteriorly. There is atrophy of the brain in the frontal region. The appearance is that of agenesis of the corpus callosum." The patient ate poorly and continued afebrile for one week. On the seventh day after ventriculographic examination, she had a severe generalized seizure, which was followed by a rapid elevation in temperature and death within forty-eight hours.

Observations at Autopsy.—The head was enlarged and showed a typical hydrocephalic configuration. The anterior fontanel was open, larger than normal and depressed. The brain weighed 1,100 Gm. The meninges were smooth and shiny and stripped easily except in the region of the right sylvian fissure. There was no evidence of subdural hemorrhage or of meningitis. The cerebral veins over both frontal lobes were larger than normal. An especially large vein was seen to emerge from the region of the right sylvian fissure. The convolutions of the left frontal lobe were normal in size and arrangement. The right frontal lobe showed great distortion of convolutional pattern and increase in size, which appeared to be due to a heterotopic mass that reached the surface of the brain in the region of the right sylvian fissure. The surface of the heterotopic mass was roughly granular, and the meninges at this point were moderately adherent. The posterior half of the surface of the brain showed polygyria and microgyria. On separation of the hemispheres, a complete absence of the corpus callosum was noted. In its place was a thin membrane of arachnoidal tissue. The septum pellucidum and the hippocampal commissure were absent. The medial surface of each hemisphere showed absence of the gyrus cinguli. The sulci were in a radial arrangement directed toward the normal site of the corpus callosum. Posteriorly, the calcarine and parieto-occipital sulci had failed to unite. The anterior horn of the left lateral ventricle was somewhat smaller than normal. The anterior horn of the right lateral ventricle was dilated. The body of the right lateral ventricle was somewhat indented laterally by an ovoid heterotopic mass, 4.5 by 3.0 cm., which was located in the region of the insula. The mass extended forward and laterally to reach the right sylvian fissure and to distort the convolutional pattern of the right frontal lobe. Coronal section of the brain through the bodies of the lateral ventricles showed the characteristic bicornuate outline of the bodies (fig. 2). The posterior horns of both ventricles were greatly dilated, with thinning of the cortex to the thickness of approximately 1 cm. The walls of the lateral ventricles presented a roughly granular appearance throughout their extent. The brain stem and the cerebellum were within normal limits on gross examination.

COMMENT

Agenesis of the corpus callosum has been observed with the greatest frequency in the first decade of life, although the condition has been reported through the ninth decade.[7] Approximately 60 per cent of case reports dealt with instances of complete agenesis. Some of the salient features of the pathogenesis, clinical picture and diagnosis will be indicated briefly. Comprehensive surveys of the literature, including clinical[8] and pathologic aspects,[9] are avalilable.

Embryologically, the corpus callosum is formed between the third and fifth months of gestation from a thickening of the lamina terminalis, a midline structure connecting the two cerebral hemispheres. Later in its development, according to de Morsier and Mozer,[9] the callosal fibers thus formed are joined to a fiber system produced on the internal aspect of each cerebral hemisphere. By the end of the fifth fetal month, differ-

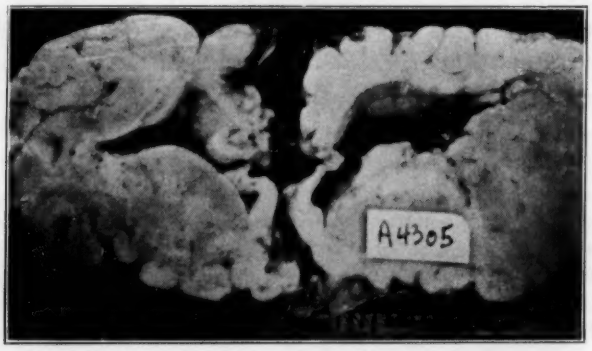

Fig. 2.—Coronal section of brain through the bodies of the lateral ventricles, showing the bicornuate outline of the bodies.

entiation is complete. The degree of arrest in development depends on the stage of fetal life in which the pathogenetic factor is operative. Variations in failure of development from complete absence of the corpus callosum to slight thinning of the posterior portion have been observed.

Intrauterine infections, meningitis or granular ependymitis occurring during the period of development of the corpus callosum were suggested as etiologic factors by some authors. Of interest in this connection is a recent report in which this anomaly occurred after a possible maternal rubella in pregnancy.[10] De Morsier and Mozer[9] listed three additional

7. Kirschbaum, W. R.: Agenesis of the Corpus Callosum and Associated Malformations, J. Neuropath. & Exper. Neurol. **6**:77, 1947.

8. Bunts, A. T., and Chaffee, J. S.: Agenesis of the Corpus Callosum with Possible Porencephaly: Review of Literature and Report of Case, Arch. Neurol. & Psychiat. **51**:35 (Jan.) 1944. Mingazzini,[2] Baker and Graves.[3]

9. de Morsier, G., and Mozer, J. J.: Agénésie complète de la commissure calleuse et troubles du dévelopment de l'hémisphère gauche avec hemiparésie droite et intégrité mentale, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:64, 1935. Mingazzini.[2] Kirschbaum.[7]

10. Friedman, M., and Cohen, P.: Agenesis of Corpus Callosum as a Possible Sequel to Maternal Rubella During Pregnancy, Am. J. Dis. Child. **73**:178 (Feb.) 1947.

types of etiologic factors which deserve mention: (*a*) neoplasms, e. g., angiomas, lipomas or meningeal cysts, developing in the vicinity of the lamina terminalis during embryonic life and mechanically hindering the development of derivative structures; (*b*) vascular lesions of branches of the anterior cerebral artery supplying the lamina terminalis, and (*c*) developmental malformations consisting of failure of union of midline structures.

A wide variety of anomalies were described in association with instances of agenesis of the corpus callosum. Their relation to the original condition is variable. Structures which develop from the lamina terminalis are almost invariably absent or anomalous in cases of agenesis of the corpus callosum; these structures are the septum pellucidum, the hippocampal commissure and the anterior commissure. Internal hydrocephalus with dilatation of the posterior part of the ventricular system is a commonly associated condition. The hydrocephalus is considered by most authors to be secondary to the basic defect rather than an etiologic agent. The internal aspect of each hemisphere usually shows a fetal arrangement of the sulci; they are radially directed toward the third ventricle. The convolutional structure of the hemispheres often shows abnormalities in size, shape and position of gyri. These abnormalities include microgyria, pachygyria, polygyria, and agyria. Convolutional patterns typical of fetal life and of the lower orders are common. A constant observation is failure of junction of the parieto-occipital and calcarine sulci. Heterotopic masses of gray matter, which consist of embyronal cells, are often seen scattered subcortically or reaching the surface. These masses are considered by de Morsier and Mozer to be evidences of defective migration of nerve cells in fetal life. It is noteworthy that visceral defects have not been observed commonly. Except for the case of thoracic stomach described by Cameron and Nichols[11] and several instances of cryptorchism, visceral anomalies have not been recorded. Cleft palate and harelip are commonly associated anomalies. They are examples of failure of union of midline structures, a type of maldevelopment which has already been described as the basis of certain cases of agenesis of the corpus callosum.

It is generally agreed that the clinical defects observed in cases of agenesis are due to the associated anomalies rather than to the absence of the corpus callosum itself. Numerous cases were recorded which showed no evidence of nervous or mental disease during life, the absence of the corpus callosum being an incidental observation at autopsy. In those cases including clinical signs of neurologic disorder, the commonest observations were mental deficiency, hemiparesis or hemiplegia and epileptic seizures. These conditions may occur singly or in any combination. The mental deficiency may vary from relative normalcy to advanced idiocy with microcephaly. Mental and motor retardation in infancy are roughly parallel. Hemipareses of varying degrees of severity were described, some with trophic changes. Hemiatrophy was seen in association with defects in development, especially microgyria, of the contralateral frontal lobe. Seizures may be generalized or jacksonian.

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11. Cameron J., and Nichols, A. G.: Partial Absence of Corpus Callosum, Canad. M. A. J. **11**:448, 1921.

Several cases of petit mal were described.[12] Chronic headaches were reported in association with some cases of epilepsy. Neurologic signs, when present, are scattered rather than focal in distribution. Electroencephalographic studies[13] revealed evidence of diffuse cortical dysfunction, with asymmetry between the two hemispheres, especially in the occipital lobes. However, students of this phase of the subject did not consider that a diagnostically specific pattern of wave changes may be differentiated.

The roentgenologic aspects of diagnosis of agenesis of the corpus callosum were first discussed by Guttmann[14] in 1929. He described enlargement of the posterior horns and of the third ventricle in the air encephalogram. The roentgenologic criteria based on the air encephalogram were formulated as follows by Davidoff and Dyke in 1934.[4]

1. Lateral ventricles are widely separated.

2. Dorsal margins of lateral ventricles are pointed or angular rather than flat.

3. Medial borders of lateral ventricles are concave.

4. Caudal portions of lateral ventricles are dilated.

5. Interventricular foramens are elongated.

6. The third ventricle is dilated and extends dorsally beyond the normal limits.

7. Air shadows cast by sulci on medial aspects of cerebral hemispheres show radial arrangement of sulci and their extension through the zone normally occupied by the corpus callosum.

This combination may be considered diagnostic. Penfield and Hyndman[5] drew attention to the bicornuate appearance of the bodies of the lateral ventricles, which they considered pathognomonic of this condition. The only condition which may be confused with agenesis of the corpus callosum from the roentgenologic point of view is a communicating cyst of the cavum septi pellucidi. The characteristic bicornuate appearance of the bodies of the lateral ventricles may then offer a clue to the diagnosis. Diagnostic criteria for the roentgenologic diagnosis of partial agenesis were outlined by Pospiech.[15]

The clinical picture of agenesis of the corpus callosum is nonspecific, since it probably depends on the pathologic disturbances that coexist with

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12. Palmgren, A., and Jonsell, S.: Agenesie des Corpus callosum durch Encephalographie diagnostiziert, Ztschr. f. Kinderh. **63**:318, 1942. Penfield and Hyndman.[5]

13. Derbyshire, A. J., and Evans, W.: A Case of Agenesis of the Corpus Callosum: Encephalographic and Electroencephalographic Studies, Harper Hosp. Bull. **1**:17, 1944. Goldensohn, L., and others: Agenesis of the Corpus Callosum: Report of a Case, J. Nerv. & Ment. Dis. **93**:567, 1941.

14. Guttmann, L.: Ueber einen Fall von Entwicklungsstörung des Gross-und Kleinhirns mit Balkenmangel, Psychiat.-neurol. Wchnschr. **31**:453, 1929.

15. Pospiech, K. H.: Encephalographische und anatomische Befunde bei angeborenen Balkenmangel und bei Erweiterung des Cavum septi pellucidi, Ztschr. f. d. ges. Neurol. u. Psychiat. **174**:249, 1942.

this condition, which vary from case to case. Air encephalography provides a means of recognizing it during life.

SUMMARY

A case of complete agenesis of the corpus callosum in an infant 6 months of age is reported. Diagnosis was made in vivo from ventriculographic examination and was confirmed by observations at necropsy. Associated anomalies in this case were fetal arrangement of medial sulci, microgyria, polygyria, heterotopia, internal hydrocephalus and granular ependyma.

Book Reviews

Pediatric Anesthesia. By M. D. Leigh and M. K. Belton. Price $5.50. Pp. 240, with 84 illustrations. New York: The Macmillan Company, 1948.

Pediatric anesthesia has become an increasingly important aspect of anesthesiology generally and of pediatric surgery specifically. Recent advances in pediatric surgery make it mandatory that anesthesiologists, pediatricians and surgeons carefully assess the anesthetic agents and technics which will be most effective in infants and children. The authors of this monograph are admirably qualified to undertake this task, and only such eminently qualified persons could have carried out their assignment in so concise and lucid a manner. The text, with illustrations and tables, has only 240 pages; yet the field is well covered.

The subject material includes preoperative preparation, physiology of respiration and circulation in children and its bearing on anesthesiology, inhalation anesthesia intubation, intravenously administered anesthesia, rectal anesthesia and local anesthesias. Choice of the anesthetic agent and technic of administration, complications during anesthesia, postoperative care, prophylaxis and oxygen and fluid therapy are also discussed. On the whole, these chapters contain essential information tersely stated. The material on preanesthetic medication is open to criticism on the basis that the doses of morphine, scopolamine and atropine employed are in excess of those indicated by the age groups in which they are employed. This tendency to overmedication of infants before operation is common practice among many anesthesiologists and is entirely without scientific basis.

While it is not the specific function of the anesthesiologist to provide for postoperative restoration of fluid and electrolyte, a chapter on this subject is included. The authors recommended Gamble's excellent monograph "Extracellular Fluid" for the reader, but, having embarked on this subject, they might have summarized more adequately the essential points in maintaining fluid and electrolyte balance in infants and children. These shortcomings are the only deficiencies in an otherwise well organized and well edited treatise on a timely subject. The monograph is current, adequately illustrated and presented in a succinct and explicit manner. It can be recommended to the anesthesiologist, pediatrician and surgeon as a valuable collection of data on the technic of anesthesia and the use of anesthetic agents in infants and children.

Oral Vaccines and Immunization by Other Unusual Routes. By David Thomson, Robert Thomson and James Todd Morrison. Price, $11. Pp. 344, with no illustrations. Baltimore: The Williams Wilkins Company, 1948.

This book is a compilation of research on vaccines, toxoids, toxins and antitoxins used by other than parenteral routes. Approximately 1,172 papers have been abstracted briefly as to results on animals and human beings. About one third of the book is devoted to oral use of BCG, owing to the large amount of research on this subject. All the common bacteria and diseases on which immunization has been attempted are covered. It seems to the reviewer that some of the conclusions drawn by the authors may have been influenced by the fact that the laboratory apparently manu-

factures vaccine commercially for physicians. In the chapter on oral immunization against colds and influenza, there is the following statement:

> **Our oral vaccine is used by a considerable number of medical practitioners in Britain, and quite a number of unsolicited letters have been received expressing satisfaction with the results of this vaccine.**

The value of this book would be enhanced if it included reference to the experimental work already done on oral vaccines. It was published for the Pickett-Thomson Research Laboratory of London. A good index of references to the literature is appended.

Your Baby: The Complete Baby Book for Mothers and Fathers. By Gladys Denny Shultz and Lee Forrest Hill, M.D. Price, $3.50. Pp. 278, with many illustrations. New York: Doubleday & Company, Inc., 1948.

This book is one of the best to appear in the rapidly saturating field of baby books. It is well written, informative and complete. The text is divided into ten parts, which, in turn, are divided into forty-five chapters. With minor exceptions, these sections are well arranged and contain a mine of useful information for the new mother.

The opening part, of seven chapters, might be considered superfluous, though no fault can be found with its contents. Few, if any, prospective parents buy "baby books" before consulting their physician because of pregnancy. Sections on "Understanding Your Baby" and "The Right Start Is So Important" are well done. A discussion of the baby's progress from month to month is especially good. A slight confusion over immunization schedules is the only fault to be found. The next three sections take up the subject of the child during the years from 2 to 6 and are excellent. "Formulas and Recipes" offers an innovation in directions for the preparation of treats for children of the runabout stage. The section on ailments and accidents is good and will help many a mother to avoid undue worry. A complete index and an overly detailed record section complete the book.

After careful reading, this reviewer can find few faults with the book. It is far above the average for books of its type.

Diabetes Mellitus in General Practice. By Arthur R. Colwell, M.D. Price, $5.25. Pp. 350, with 30 illustrations. Chicago: The Year Book Publishers, Inc., 1947.

This first volume in a series is a concise, practical book for any one interested in diabetes. The author has extensive experience in both the clinical and the investigative field. He recommends the weighed diet for all patients, especially in the early phases of the disease. The references to the disease in children emphasize the universal need for insulin, the weighed diet and the instability of diabetic management. There is a brief discussion on pregnancy and diabetes which is of interest to the pediatrician.

News and Comment

NOTICES

Course in Pediatrics for Specialists Announced.—From Feb. 7 to 12, 1949, the Tulane University of Louisiana School of Medicine, Division of Graduate Medicine, will give a course in pediatrics for specialists. Those desiring to take this course should apply to: Director, Division of Graduate Medicine, 1430 Tulane Avenue, New Orleans 12.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Bornehospital, Copenhagen, Denmark.

Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.

Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.

Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.

Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.

General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Asociacion de Pediatras de Cataluna

President: Dr. Emilio Roviralta, Policlinico, Platon 1, Barcelona.

Secretary: Dr. Francisco Llaurado, Via Layetana 23, Barcelona.

Associacao Paulista de Medicina, Seccao de Pediatrias

President: Dr. Armando de Arruda Sampaio.

First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.

Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.

Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.

Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.

Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.

Time: Concurrent with the annual conference of the Chinese Medical Association.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

DANISH PEDIATRIC SOCIETY

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjorup, Dronning Louises Bornehospital, Copenhagen.

NEDERLANDSCHE VEREENINGING VOOR KINDERGENEESKUNDE

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1, Time: Fourth Friday of each month, 4:15 p. m.

SCHWEIZERISCHE GESELLSCHAFT FUR PADIATRIE

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Prof. Dr. Luis V. Sotelo.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: Casilla de Correos 12, La Paz, Bolivia.

SOCIEDAD CHILENA DE PEDIATRIA

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

SOCIEDAD CUBANA DE PEDIATRIA

President: Prof. Augustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRIA DE CONCEPCION (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.

Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRIA DE CORDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.) Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRIA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores Chacin, Sur 17, No. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIETE DE PEDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY
SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. John A. Toomey, City Hospital, 3395 Scranton Rd., Cleveland 9.

Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION
Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY
President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN
President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH
President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY
President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY
President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY
President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY
President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY
President: Dr. John M. Nelson, 1558 Humboldt St., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS
Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Place: Miami, Fla. Time: October 1948.

STATE

ALABAMA PEDIATRIC SOCIETY
President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6.
Place: Montgomery, Ala. Time: September 1949.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SECTION

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.
Place: Philadelphia. Time: Oct. 4-7, 1948.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Gerald C. O'Neil, 116 S. 49th Ave., Omaha 3.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Samuel Ravenel, 371 N. Elm St., Greensboro.
Secretary: Dr. Charles Gay, 1521 Elizabeth Ave., Charlotte.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY

President: Dr. Charles B. Alexander, 1716 Nix Professional Bldg., San Antonio 5.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Thomas Gibson, 114 W. Boscawen St., Winchester.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION OF PEDIATRICS

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.

Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Tine: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Harold T. Vogel, 3420-86th St., Jackson Heights, N. Y.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

CHICAGO PEDIATRIC SOCIETY

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

DALLAS PEDIATRIC SOCIETY

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13. Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708 Fifth Ave., Pittsburgh.

Secretary-Treasurer: Dr. C. J. Soecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

PORTLAND (ORE.) ACADEMY OF PEDIATRICS

President: Dr. Scott Goodnight, 1020 S. W. Taylor St., Portland 5.
Secretary-Treasurer: Dr. Carl G. Ashley, 2455 N. W. Marshall St., Portland 10.
Place: University of Oregon Medical School Library. Time: 8:00 p. m., first Monday of each month from September to June, inclusive.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. V. E. Hrdlicka, 7424 Cromwell Dr., St. Louis.
Secretary-Treasurer: Dr. Don L. Thurston, 21 Cambridge Court, St. Louis 22.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.
Place: University Hospital, Ann Arbor. Time: Oct. 29-30, 1948.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).